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TREATMENT OF NEURASTHENIA.*

By Austen Fox Riggs, M. D., Stockbridge, Mass.

No more startling diversity of opinion is to be found in any field of modern medicine than that which obtains in the realm of the so-called "functional nervous disorders." Order has been brought out of chaos in almost every other department, and treatment of symptoms has consequently been replaced by treatment of conditions, based on a sound understanding of the etiology and pathology of these conditions.

But of the functional nervous disorders the pathology is thus far purely hypothetical, for practical purposes non-existent; and the etiology still resides in the realm of vague speculation. Take, for example, that much-worn label, "neurasthenia"—under it we find the following salad of definitions:

Dana, in the 1908 edition of his book, defines it as "a chronic functional nervous disorder characterized by a morbid weakness and nervous irritability."

Burr, in Osler's System, 1910, says: "Primary neurasthenia, strictly defined, includes only a condition of pathological weakness without discoverable lesion."

Starr says, in his book of 1913: "It is a condition of exhaustion of the general nervous system, general or local"; and quotes Edinger, who believes in the cell exhaustion theory with secondary sclerotic changes.

McCarthy, in Hare's Therapeutics, 1911, says: "Essential neurasthenia may depend upon either a congenitally inefficient nervous system, or upon abuse of the nervous system."

White and Jelliffe, in their treatise, edited by Jones, in 1913, say, among other things: "It is a fatigue neurosis due to onanism." Whereas Church, in Church and Peterson's text-book of 1914, says: "It may be due to continence," and defines neurasthenia as "a nervous state marked by irritable weakness, where nervous energy, both psychomotor and organic, is reduced, so that there is less endurance and consequently more irritability."

Barker, in Forcheimer and Billings' Therapeutics, of 1915, says: "Neurasthenic and psychasthenic states are mild forms of mental disorder, and are so-called functional nervous diseases, separable from organic." He points out, however, that this is an arbitrary division. He says: "There may be material changes in the nerve cells, but too much stress should not be laid on this view." "These conditions," he further adds, "are not to be regarded as diseases *per se*, so much as nervous and mental syndromes, that is, abnormal mental attitudes and reactions."

I hesitate to swell this confusion by adding to it the hypotheses of Freud and his followers. I am quite willing to let them pass with mention, as it would not serve our present purpose

* Read before a meeting of The Johns Hopkins Hospital Society, May 3, 1916.

to enter the unnecessarily bitter discussion which rages about their theories.

At least one has a liberal choice of hypotheses, and so can feel perfectly sure that he will have good company, whichever one he chooses.

It is no wonder, then, that there are almost as many varieties of treatment for neurasthenia as there are physicians or quacks who practice the gentle art of healing these unfortunates! I feel, therefore, very little hesitancy in setting forth, in some detail, my own brand of treatment for neurasthenia; for I know, without further reference to the literature, that at least one author from among the best will be found to lend me the comfort and support of his authority.

Eight years ago, when I began to limit my practice to treating nervous cases, finding so many contradictory hypotheses in regard to neurasthenia, or, to put it more politely, having such a very wide field to choose from, I was at a loss; so I did not choose at all, but determined to use empirical methods, and to let my hypothesis grow by experience. Thus I bent my energies toward trying to understand the personality and needs of each patient. This intensive study of the individual patients included a study of their histories from an etiological viewpoint, the effect of previous treatments, and also the effect of my own treatment, which was at first guided largely by the "cut and try" method. Upon data and impressions thus obtained, rather than upon the authority of the literature published on the subject, has my conception of neurasthenia and its relations grown, and the Stockbridge treatment been developed.

I am considering neurasthenia as covering psychasthenic and hypochondriacal sub-varieties, for I do not find any fundamental difference in these sub-varieties.

As distinguished from the psychasthenic, the neurasthenic is simply the type that is annoyed and needlessly incapacitated by his exaggerated sensations, and therefore refers his symptoms to his body.

The psychasthenic, on the other hand, though belonging to the same general category, is too acutely aware of his mental processes, is annoyed by his emotions, and therefore refers his symptoms to his mind.

The hypochondriacal variety seems to me to be an exactly similar breed of cat, and may belong to either type, but with the worry and fear element sufficiently predominating to change the clinical picture—but only superficially.

All three are the same fundamentally.

A short statement of the hypothetical conception of the nature of the disorder under discussion, as well as a brief account of the data upon which it is based, may properly precede the description of the treatment, which in turn is, I hope, the logical outcome of the former.

In studying the treatment received by my patients before coming to Stockbridge, it was soon borne in upon me that prolonged rest had regularly done them more harm than good. In fact, the more rest they had had, the more tired they seemed to have become. Indeed, many of them were all tired out resting!

On the other hand, those who had had an exercise cure were in much better condition, not only physically, but mentally as well.

Temporary results of a striking sort had, of course, often been wrought by successful treatment of this or that complicating physical condition, such as malpositions, constipation, dyspepsia, intestinal absorption, malnutrition, etc. But all these good results were striking chiefly because of their short duration and the insignificant effect they had had upon the fundamental nervous condition. A neurasthenic with a fallen stomach became the same neurasthenic with an uplifted stomach.

My patients always seemed to have derived greater and more lasting benefit from psychotherapy, regular or irregular, than from any variety of physical treatment. Ignominious to our noble profession is the fact that the orthodox forms of physical treatment, whether rest, exercise, or orthopædic, were markedly less potent than the quack, fake physical cures, because these latter are regularly so much richer in suggestion, in the emotional stimulation of hope, and in the guarantee of faith, than are our more respectable methods.

Furthermore, the physical conditions complicating my cases proved to be of such an infinite variety that it seemed to me absurd to suppose that they could be causal. That a practically identical condition, namely, a psychoneurosis of the neurasthenic or psychasthenic type, should have resulted from a totally different physical cause in nearly every case, was not a practical hypothesis; so it died a natural, though lingering, death. In other words, whatever the physical disorders might be, it seemed clear that, both because of their unending variety and because of the negligible effect that even successful treatment of them had had upon the ever-present nervousness, they had to be considered as merely complicating or secondary occurrences.

Save for the above-mentioned mild disturbances of bodily function, a thorough physical examination of these patients discovered absolutely nothing abnormal. Clinical laboratory examinations yielded, with like exceptions, negative results as well. Even the much-maligned nervous system came through the ordeal of examination with absolutely consistent victory. Objective symptoms were always wanting. Subjective symptoms, regularly, more than made up the deficiency by being present in overwhelming numbers. Such objective symptoms as did occur always varied with each different case, whereas the subjective symptoms seemed to have a common brotherhood—a sort of family resemblance. Each succeeding case made the evidence grow stronger. Its accusing finger pointed less often to the body, until it finally rested with unfaltering constancy on the mind as the guilty element.

The therapeutic mistakes of others, as well as my own errors, served only to strengthen this suspicion, and the result of changes in my own therapy finally brought about the absolute conviction that *neurasthenia is a mental disorder,* and that it should be attacked primarily as such.

Studying the statistics of my cases, I am unable to find any reliable or undeniable predisposing causes for neurasthenia.

In the family histories, insanity, alcoholism, organic physical diseases, such as rheumatism and tuberculosis, appear with just about the same relative frequency as they do in the case histories of a general medical or surgical practice. But nervousness in one or both parents occurs in 52.4%; nervousness + insanity, in 2.7%; + alcohol or drugs, in 0.3%; + constitutional diseases, in 6.9% = 76%.

A study of the occupations brings to light nothing of interest —not even a suspicious absence of occupation, much as this fact would disappoint the railers against "nervous prosperity."

As far as sex goes, in my practice the women lead the men in the proportion of three to one. However, I do not think that one can conclude from this that the condition is a difficulty exclusively or peculiarly of the gentler sex, for the average woman can leave her job temporarily with less risk of losing that job than can the average man, and this may be the reason for their predominance in my practice. Dana and Starr both state that men predominate, while other authorities call the sexes even. However, in my opinion, if it be true that women are more frequently victims, it is not because of anything intrinsic in their make-up, but because they are usually less well trained mentally than men, and therefore more apt to lose their equilibrium. (Three-fifths of my patients belong to the well-to-do class.)

As to age, neurasthenia, like other forms of functional disorder, and by this I mean disorders without gross or discoverable lesion, occurs in late adolescence and early maturity with greatest frequency. The reason for this seems to me to be that at this time of life the individual is called upon to adjust himself or herself most radically and most frequently to the changing physical and mental needs and impulses of life; is called upon to use greater skill in self-guidance, and is, therefore, more apt at these times, so to speak, to run off the tracks of normality. Of my patients, 56% were above 20 and under 50 years old, the largest number, 33%, between 30 and 40, when they applied for treatment.

I have found neither physical nor anatomical conditions peculiar to these cases. The lean possibly predominate over the fat. But then worry, the neurasthenic's special privilege, is a notorious reducer, and is an almost constant element in this disorder.

A very frequently recurring factor among the possibly predisposing causes is the personality of the patient. Something like 80% of them speak of their "temperaments" as causal. "Sensitive" or "high-strung" are the terms most commonly used by them and by their friends, and I think in the main that they are right, for temperament, *i. e.*, mental personality, is at least one clew to the situation.

So, for possibly predisposing causes my search yields only—neurasthenic parents; a time of life when changing conditions of life call for radical readjustments; and, lastly, mental personality or temperament.

Neurasthenic parents may not mean that neurasthenia is inherited. The children of these parents have lived with their parents, in the vast majority of cases, and have therefore lived under the influence of their intimate example, open to the mental contagion of their behavior, during the most impressionable, the most suggestible, period of life, when habits of mind are formed. So it is at least a fair assumption that the parental neurasthenia has had a great, even if not the only, effect on most cases as an environmental element.

This individual peculiarity called "temperament" must, of course, be accepted as the resultant of these two forces, heredity and environment, whatever their respective relative proportion may have been in any given case. I only wish here to suggest that the frequency of neurasthenia in the family history does not necessarily mean that there is in all, or even in a majority, of such cases a hereditary taint.

Indeed, it is my belief that, like greatness, only some are born neurasthenics, whereas the greater number have it thrust upon them, by unwise training and adverse conditions of early environment, or, more rarely, bad environment in later life.

Exciting causes, according to the patients, are many, and in each case quite definite. Each case has its own pet cause. But the variety—the immense variety—to be found in the aggregate, bars any one of these conditions from the ranks of reliable causes. Often a patient will date his breakdown from an operation. It is frequently a clean appendicectomy or some uncomplicated surgical procedure. But if one searches the history with care, one regularly finds that there have been a number of neurasthenic symptoms far antedating the operation—often a series of distinct breakdowns, the operation merely being the convenient opportunity for the neurasthenia to express itself frankly.

Of course, very severe illnesses and severe operations, especially when they mean weeks and months of invalidism, and also severe mental shocks, do produce cases of secondary neurasthenia. But even in such cases one wonders if the underlying neurasthenic predisposition has not, after all, played the chief causal rôle, while the severe illness or operation has played the louder and more noticeable one of opening the gates and thus bringing the formerly unrecognized condition to the surface.

Shocks, losses, unhappiness, and difficulties—either mental or physical or both—are certainly no more frequent in the histories of these people than they would be in the life stories of any group one might pick out in an ordinary community. In fact, I have often been struck by the opposite! Usually my patients have been extraordinarily well supplied with the materials of happiness, only just seasoned with the ordinary difficulties.

There are, I believe, a great many more people who go through illnesses, undergo surgical operations, meet the ordinary and extraordinary difficulties of life without developing neurasthenia, than there are neurasthenics all told.

In short, I do not believe that the fundamental cause of the disorder can be found in the quality or quantity of the environmental stimuli. Nor yet in any physical peculiarity, anatomical or physiological. It must lie in the way these patients respond not only to the extraordinary, but chiefly to the ordinary, difficulties of life.

It seems inevitable, then, that the real cause must reside in some mental peculiarity common to all these patients. I believe that in some cases this peculiarity is directly inherited, and that in most cases a perfectly normal individual acquires it very early in life by direct mental contagion from neurasthenic parents or relatives or attendants. In still others, and more rarely, it may be produced later in life by a normal individual reacting to extremely abnormal physical or mental strains. To this last type belong the cases rightly called *secondary neurasthenia.*

My conclusion, then, is that neurasthenia is primarily a mental disorder; that the disorder, in nearly all cases, is originally independent of any and all bodily conditions, and that it exists, of course, in spite of a structurally normal central nervous system.

The mental peculiarity is in part a sort of "tenderness." (William James.) It is characterized by abnormal mental sensitiveness to the quality of feelings. Pleasantness and unpleasantness, especially unpleasantness, is too important. Therefore, sensations acquire an abnormally high emotional value, and also, through malinterpretation, a false significance, and both they, and likewise the emotions themselves, become, one might say, chronically and exaggeratedly accentuated. This chronic sensory and emotional overtone leads directly to mental inefficiency, for feelings, not reason, become the rulers of action, and the expenditure of energy is turned into abnormal egocentric channels and is accomplished at a wasteful dead level of intensity. These patients always use a sledge hammer to drive a tack, or to crack an eggshell. This inefficiency, of course, results in the characteristically poor adjustment of the individual to his environment.

The neurasthenic's world becomes divided into affective categories—things and people that are unpleasant and things and people that are pleasant; things which do him good, and things which do him harm; things which require effort, things which do not. The effortful, unpleasant, possibly harmful, are contrasted with the uneffortful, pleasant, and possibly beneficial. Ambition is replaced by caution, and life becomes a fear-ridden, retreating pilgrimage, self-conscious and miserable, whose chief, if not only, object is self-preservation, not from death, but from some great bugaboo, such, for instance, as that commonest of all symptoms, "fatigue," falsely so called, and really only a heightened consciousness of bodily sensations, concentrated and colored by apprehension.

The chronically heightened emotional tone over-drives or inhibits one or many of the bodily functions, and thus the functional disturbances so familiar in these cases are established. These are usually accepted, not only by the patients, but also, I regret to say, too often by their physicians, as the fundamental causal conditions, rather than as by-products, which they really are.

Crile and Cannon have severally shown how these functional disturbances are produced in animals, by emotion acting probably through over-stimulation of the suprarenal and thyroid mechanisms.

To all intents and purposes, then, the neurasthenic is an organically normal individual. He is sound of mind and body, but this normal apparatus of his gets out of working order because it is unskillfully used and, therefore, gets out of internal adjustment, and also out of adjustment with what should be its work.

A study of the effects of various forms of treatment confirms this view. *Were neurasthenia exhaustion, rest would cure it. It does not.* Forty-nine per cent of the cases which this report covers had received definite "rest cures" before coming to Stockbridge, but still remained neurasthenic.

Were it an *inherent weakness* of the organism, not a single case could be cured. Many cases are cured.

Were it *due to physical disorders,* then physical treatment of these disorders would cure it. Physical treatment has served at best, in my experience, to change only the physical by-products. Of the cases here reported, about 50% had had dietary, orthopædic, medicinal, calisthenic, hydrotherapeutic, or other physical measures combined with rest cures, while some 10% had had these measures without a rest cure.

Even in the secondary type of neurasthenia, when its physical cause has yielded to physical treatment, the neurasthenia is very apt to pursue its course unless directly and properly treated for itself.

The conclusion seems clear that neurasthenia is not weakness nor exhaustion; that it is neither a malady of the intestines, the heart, the stomach, nor a disorder dependent upon structural change of the nervous system; and that it, therefore, cannot be cured either by rest or by any other physical means.

The conception, then, of neurasthenia which I have drawn from experience, and which I hold as a working hypothesis, is that it is a mental disorder, probably without organic structural change, characterized by emotional overtone; by egocentricity or, more graphically, by an ingrowing attention; by mental inefficiency; by a consequently poor adjustment of the individual to his environment; and, lastly, by a great variety of disturbances of bodily functions, which item, in common with all the others, acts retroactively upon all of its fellows. Truly a typical vicious cycle!

It calls for psychotherapy primarily and for physical means only secondarily, and then only to combat the physical by-products—whatever they may be.

Psychotherapy is of many brands. I have found formal direct suggestion of very little use, save to remove such symptoms as were produced by suggestion. It seems to me to be a very inefficient and crude method and rarely, if ever, touches of itself the basis of the trouble. It is essentially a symptomatic treatment (of use chiefly in hysteria).

Informal indirect suggestion is a far more flexible instrument, but one which every intelligent physician does and should use, whatever his practice. It is, of course, only an adjuvant, though an important one, to one's main psychotherapeutic efforts.

Psychoanalysis carefully, scrupulously, guarded by common sense against the personal bias, the personal symbolism and

the possible sexualism of the user, is a very useful diagnostic instrument.

We have Freud, his co-worker, Jung, and their followers, to thank for the possibilities which this method has opened to us. But his own personal symbolism, which, as it reveals itself in his work, is so repugnant to many of us in its oriental sexualism, has prejudiced us against Freud's methods. Exclude this prejudice, and with it the hypersexual symbolism, and we find much that is valuable in this method. But a so-called "thorough Freudian analysis" I have no use for. It has in several cases to my absolute knowledge done great harm—harm which in one case it took two years to remedy, though the analysis had been applied by a distinguished Freudian over a period of some two years.

At all events, I have found in psychoanalysis, when thus guarded, a valuable diagnostic tool, especially in that most important matter, the study of personality; and it frequently either blazes the way for the active therapeusis or guides it on its way.

Fundamental re-education of the patient is the weapon in which I put my greatest trust. To teach the neurasthenic what neurasthenia is, to teach him to contrast this state of mind with the normal, to show him that he can attain this normality, is, I believe, 75% of curing him. The other 25% consists in applying this knowledge to practice.

Coupled with the re-educational psychotherapy there must, of course, be rational physical treatment, based on the particular need of each patient. This part of the treatment is carried out in Stockbridge according to a definite schedule for each patient, in which exercise plays an important rôle and includes individual calisthenics, as well as out-of-door walks, golf, skating, or snow-shoeing; while rest plays a distinctly subordinate part, and is given no physiological importance whatever.

Only for complete physiological bankrupts should rest be at all an important item and, even in these cases, I have never continued it at an aggregate of over three hours daily, exclusive of the night, for more than a week or ten days. Rests, though short, should be made as perfect in quality as possible; that is, patients should be taught how to rest. In other words, they must learn how to free, not only their bodies, but also their minds from their own pernicious over-responsible and tense control.

This part of re-education is especially important for those who suffer from the syndrome called insomnia, which is no more, no less, than a fear of not sleeping, a nocturnal apprehensive restlessness, which is the cause, not the effect, of the sleeplessness.

Rests, then, are considered rather as object lessons in re-education, illustrating what non-interference and non-responsibility will do, than as important physiological items.

Occupation, both manual and intellectual, I consider one of the most important instruments of re-education, for through it one can teach efficiency more objectively and more directly than, perhaps, by any other method. For by studying a patient's way of working, one can actually see the faults in expenditure of energy and correct them, so to speak, on the spot.

In Stockbridge we find that weaving for women and wood-carving or cabinet work for men answer the purpose admirably. Intellectual occupation, on the other hand, is varied more according to each patient's personal resources and needs. Reading, coupled with analytical summarizing, is a frequent prescription, the work being preferably on a subject closely allied to the patient's normal job.

As I have said, re-education is the method upon which we place our greatest reliance. This is carried on through a series of office visits, which are never hurried, and are therefore frequently pretty long—they average an hour, I should think. At first, until the patient is well started on his schedule, a daily visit seems best. Then one every two or three days is sufficient.

A thorough physical examination precedes treatment. I mention this, not because of the obvious fact that it is an essential preliminary to any treatment, but because I consider it the fundamental starting-point of the therapeutics of re-education, especially from the patient's point of view. A pupil must know that his teacher is himself personally familiar with the facts, otherwise he cannot be expected to have any real confidence in the teaching. This examination is also purposely and patently made the direct basis of the physical regimen prescribed, and it thus serves another obvious therapeutic purpose.

The relation of teacher and pupil being at least fairly well established, re-education proper is begun by a few explanatory talks on normal physiological psychology, without at first any reference to the patient's especial difficulties.

These talks deal with the nervous system reduced to a very simple diagrammatic form, in which it is pictured as a telephone system with the brain as central office, while consciousness is considered as made up of energies transformed and liberated by this mechanism.

As this preliminary part of the re-education is based on a definite mechanistic conception of consciousness which also expresses to a large extent, and in some detail, my own conception of the nature of neurasthenia, I am going to quote liberally from a series of pamphlets which contain in summarized form the descriptions referred to. They are written as text-books to patients, to summarize and make concrete the re-educational talks.

The first pamphlet, after describing the nervous system, and tracing a simple sensory-motor reaction, goes on as follows:

For the purpose of description, then, let us consider the field of consciousness as though it were a sheet of water, the borders of which we know by inference must exist, but which we have never seen and probably never shall see, and whose depth likewise is immeasurable. The surface of this sheet is covered by waves of various sizes, shapes and colors, and, unlike the waves of the real water of our terrestrial seas and lakes (which move in ranks and owe their size and motion to the direction and intensity of the wind), these waves are arranged in groups, the groups in families, the families in constellations, and the constellations in one great coordinated system. In this figure, each impression made upon

our consciousness from the time of birth to the present moment, is represented by a wave, and the waves are arranged in groups and systems, according to the laws of association. (This group may be made up of impressions received at a certain time, and constitutes the memory of an event; that group, of impressions having the same or similar emotional content; and the next group may be held together by some other bond of similarity.)

These groups and individual waves are in continual motion, that is, there is motion within the groups and also a general ebb and flow of the larger or smaller combinations across the whole field. Part of the movement is due to the continual formation of new combinations from the old. This group or that may dissolve and its component parts join other groups, or the central wave of one group may leave it to become one of the subsidiary waves of another group. (For example, if the objective of the consciousness of the moment be the construction of rhymes, loss, boss, toss, dross, coarse, may group themselves by similarity of sound around cross, whereas, were the objective changed, cross by similarity of ideas might become the central idea or wavelet of another group composed entirely of ideas dealing with religion.)

The wavelets in the further regions are more stable in their grouping. Those belonging to the stomach, for instance, are closely and permanently bound together, as are all those belonging to the knee-joint or the heart or the intestines. Waves that have to do with happenings in the past, especially with forgotten scenes and incidents, are also closely associated, and, when they migrate, move not singly, but as groups. This changing and rearranging is most active in the central part of the lake, is most inactive as we approach the borders.

Now assume that the whole sheet is in total darkness save that at or near the middle portion there is a light suspended from above, which illuminates a very small area. It is a mere pencil of light, capable of illuminating but one wave at a time, but it has the faculty of very rapid motion, and is thus capable of illuminating a good many waves in such quick succession that it produces the effect of having illuminated them almost simultaneously. This light represents the attention. To carry out the figure, we must imagine ourselves suspended above it and as being able to control its direction by our will. Just as the searchlight of a battleship has a definite range beyond which the light does not reach, so the light of our attention can be projected over only a limited area of the sea of consciousness. All that lies outside this area, at any given moment, is, for that moment, subconscious—so that we speak of that portion of consciousness outside the range of the attention as the sub-consciousness and that portion which lies within the illuminated area as the consciousness; or, more accurately, the former is called the unaware consciousness, and the latter, the aware consciousness.

Bearing in mind the continual motion of the waves, we may picture them as coming single file and in groups, from the darkness into the light, and passing from the light out into the darkness again. One wave brings others in its train, and in the order of their associative values; and impelled by the object of the moment, we direct the light of our attention in a selective way upon the passing throng.

That sensations, real sensations, may make their impressions and become associated with other sensations without ever reaching the light of the attention—that, in other words, they can do this without our knowledge, is a factor of the greatest importance in understanding the hidden dynamics of our consciousness.

It is safe to say that there are a thousand times as many sensations recorded in the field of consciousness as are ever recognized, or, in other words, of which we have ever become aware. The fact of sub-conscious sensations, though an odd one at first sight, explains the many coordinate movements and automatic actions that without this explanation would remain mysteries.

Each family of waves may be said to be made up of two subgroups; one of which, comprising the waves representing, for instance, the sensations of position, of vibration, and the deep muscle and tendon sensations, is a stable, stay-at-home cluster which normally always remains in the sub-consciousness. The other sub-group, which includes the sensations of touch, pain, and temperature, is more mobile, more loosely held together, and thus, any of its members are easily drawn from the family circle into the aware region. Any of these mobile sensations become very easily accentuated by the ordinary physical stimuli of the environment, and are thus constantly flashing in and out of the attentive region. Even without physical accentuation, one or more of them may be drawn to the attention, if one simply thinks of this or that part of one's body, and, consequently, at once becomes super-conscious of it.

Bearing this mechanism in mind, it is easy to see that sensations in this class, after being repeatedly picked out and dwelt upon by an otherwise idle attention, will form a most unwelcome habit of finding their way with greater and greater ease into the aware consciousness, and that consequently they will become exaggerated through repetition and over-attention. This process, in fact, plays an important part in the genesis of nervousness, where the sufferer becomes abnormally aware of many, one might almost say of all, of his sensations (and it also plays no small rôle in numerous other sorts of "nervousness").

There is another accident which may occur in the mental field which produces a similar result. Not only may the mobile sensations of the "touch" class, of which we normally may or may not be aware, become accentuated and exaggerated, but even those sensations of which we are normally never aware, namely, those belonging to the stable, sub-conscious group, may, under certain circumstances, reach the light of our attention. This they do by virtue of a process of disassociation, that is, by a breaking up of the normal arrangement of sensations in sub-groups and families. Thus, when a family of sensory waves becomes accentuated (although usually only the more mobile sub-group of the touch and pain class is affected), provided that the mental constitution be liable to disassociation, the lightly balanced associative values of a whole family may be upset. The result is that one or more sensations of the stay-at-home group, which should have remained quietly at home in the subconsciousness, now disassociate themselves from this, their normal cluster, and promptly join the other sub-group of the family. They then assume the habits of their new companions and wander with them into the illuminated area. Thus, not only does the "touch" sensation become prominent, but it drags with it into the aware field one or more of its normally sub-conscious brothers. Here, of course, the latter literally "make a sensation." They wear the uniform, let us say, of the knee family and are therefore recognized as hailing from the knee country; but this is the only familiar characteristic they possess, and they are above everything fascinating to the attention because of the utter strangeness of all their other qualities. They are out of place—as startlingly out of place as fish out of water. The sensations are perfectly normal in themselves, but they are distinctly and markedly abnormal in their relative position in consciousness. Like deep-sea creatures suddenly hauled gasping to the surface, they are out of their natural element, the quiet sub-conscious regions, and are showing themselves in the utterly strange environment of the intensely active and brightly illuminated aware region. Of course they seem unnatural, undesirable; and furthermore, we treat them with fearful attention and respect, because they seem to signify that there is something very strange going on in the bodily region from which they emanate. The sufferer little realizes that their abnormality consists chiefly in mal-position, and not in intrinsic quality or significance.

Once having gained the entrée, the dislocated sensations in question very soon acquire the habit of calling with always greater frequency and familiarity. Naturally, the attention dwells with greater and greater intensity upon its strange guests, and the latter consequently swell to an enormous importance. Before long the secondary physical results make their appearance. The function over which the sensations in question formerly presided without let or hindrance now suffers over-stimulation or over-inhibition, as the case may be. The sensation, because of its abnormal activity and also because of its malposition in consciousness, has attracted more than its share of the attention and the latter consequently interferes with the nervous control of the function.

Then follow examples of bodily functions so disturbed. I will quote only two—fatigability and dyspepsia:

The candidate for this malady may have his attention drawn to his gastric sensations in any one of a variety of ways. An acute but passing indigestion, following some indiscretion of diet, may accentuate these feelings sufficiently to turn the trick. The reading of a patent medicine folder—which is usually a masterpiece of graphic description—may cause him to search his consciousness for the presence of any of the sensations described, and the search rarely fails to yield an ample regard. The sensations, however they may reach his attention, when once they have done so, are only too apt to become frequent visitors—this being almost inevitable, if he has been born with or has acquired the hypochondriacal tendency.

Beside these sensations, one or more of the sub-conscious stay-at-home group of the same family may join the procession. Whether this happens or not makes only a difference of degree in the result, and in either case, when once the sensations have engaged the attention sufficiently, the quiet autonomy is destroyed. The gastric functions are inhibited or stimulated, as the case may be, by the effect that the attention has had upon them in interfering with the quiet interchange of sensations and motor impulses which previously presided undisturbed over them in the outermost sub-conscious regions. Consequently, too much or too little gastric juice is secreted, or the muscular action of the stomach is affected, and an actual chemical and mechanical disorder is established. The disturbance of gastric function then becomes responsible in itself for additional sensations which are abnormal not only in intensity, but also in quality. The latter do their part in further disturbing the harmonious automatism that should exist—worry does its share—and so the dance goes on.

Fatigability is one of the most prominent symptoms in "neurasthenia" and the one most often complained of. The latter fact probably has had no little effect in fixing the popular misnomer—nervous *exhaustion*—upon this malady. As a matter of fact, fatigability is itself a misnomer, for the neurasthenic suffers not so much from true fatigue as from an overwhelming apprehensive *sense of fatigue*.

The genesis of this star in the galaxy of nervous symptoms is much the same as that of the preceding example (see dyspepsia). The patient, however, instead of suffering from the accentuation of merely a few sensations of the mobile class, or from intrusion into consciousness of a few others which normally should remain sub-conscious, becomes unduly aware of a great many sensations of both kinds and from nearly every part of the body. The attention is of the "ingrowing" type, sharpened to appreciate the slightest sensory changes, and thus that flood of sensations which is continuously pouring into the sub-consciousness in every one, and in normal people remaining there, is encouraged and indeed invited to overflow into the aware region on the slightest pretext. These sensations when they become conscious are vague, unnatural, disagreeable. They are not clean-cut and familiar, as are those of pain or heat or cold, but they form a jumbled mass, without outline—without beginning or end. The sufferer does not experience the more or less comfortable, soporific sensations of the true fatigue that follows a 20-mile tramp, or comes as a natural result of a good day's work. On the contrary, the victim of fatigability feels as though his mind and body had been transformed into a seething mass of sensations and finds himself in a very agony of aching confusion. Quiet and rest, if he is still able to rest, will give only temporary relief, and for this very reason rest is sought more and more frequently and for ever more protracted periods, and with always less relief as the case progresses. The sufferer becomes more sensitive to the fatigue-like feelings—his attention becomes more exclusively occupied by his sensations, and consequently becomes more difficult to control. For this reason it actually requires more energy to hold the attention upon any outside matter and, therefore, in performing a given task, he suffers an actual and disproportionate mental fatigue, which adds its effect to the sensory turmoil. Furthermore, his sensations lead him into more and more pronounced physical indolence, varied only by absurdly heroic spurts of effort, and this very naturally results in the muscular weakness which always follows disuse, as well as in general sluggishness of nearly all of the mechanical and chemical functions of the body. Worry as to the outcome of the disorder and the emotional disturbances centering about self-pity are the links which complete the chain of the vicious cycle.

Only after a fair working knowledge of the human machine in order has been attained and the genesis of nervousness in general, as a disorder of the mechanism, is thoroughly understood, is reference made here and there to one or more of the particular symptoms complained of, but these are treated largely as illustrating the lessons, and as interesting only from this point of view, rather than as important items in themselves.

Next, the re-education deals directly with the abnormal condition and only through it indirectly with the more troublesome symptoms of the case, explaining their nature and genesis when possible. The condition which they signalize bears the emphasis and its cure is the main theme. Every effort is thus made to help the patient to evaluate his symptoms by rationalizing them and then giving him reasonable grounds upon which to shift his interest and attention away from feeling to action.

Such evidence as can be drawn from the patient's actual current experiences in following out his schedule is, of course, utilized to demonstrate the principles discussed and to make the theoretical re-education square with practical application.

From first to last, every effort must be made to change the point of view of the patient from that of morbid egocentricity to one of a healthful, positive purpose in life. Objectiveness must take the place of subjectiveness, ambition and courage must replace introspection and fear, and the patient must be taught that it is his right and duty to demand quiet and efficient service from his body and mind. He must realize that they constitute an apparatus which is the means, not the end, of life. The philosophy of acceptance must be accepted as the basis of rest and as the starting point of work, while the ideal of service must be made to crowd out the idea of self-preservation.

Re-education must include this revivifying of normal ideals, for the whole structure of physical and mental training would collapse without its object—normal life.

I have been struck in some instances—fortunately they have been few and I believe entirely the fault of my own technique—in which the labor of re-education and re-normalization of physical functions was wasted, and the patients soon slumped to their original subnormal condition because these necessary ideals were not forthcoming. The whole process, being thus without object, was foredoomed to failure.

The physical part of the treatment is carried out, as I have said before, according to a schedule (individual for each patient) in which the elements of exercise, work, recreation and rest are definitely stipulated, and as nearly as possible in the normal quantity and normal relative proportion.

As soon as the patients have acquired a good working modicum of self-control, and their physical condition has become satisfactory—with as little warning beforehand as possible—they are sent home on a trial trip, to apply their knowledge and the fruits of their practice to their own environment. The stay at home varies from two and three weeks to six months or more in length—according to the case and the environment. A return to Stockbridge for treatment usually follows the trial trip. It is in most cases short—a few days only—and usually consists in a critical review of the successes and failures in adjustment, and other experiences, brought out by the trial trip. The next home-going is apt to be permanent, but is often followed in six months or a year by another and final visit of a few days in Stockbridge.

In the milder cases, this series of trial trips is not necessary, but all cases, even these, are kept track of for 18 months or two years after discharge by means of reports written by the patients at regular intervals.

Results do not prove that an hypothesis is correct, but they are at least apt to be suggestive of its success or failure as a working hypothesis. Therefore, I beg to conclude this account of the Stockbridge treatment with a summary of results obtained. It is doubtful whether the treatment would have given better results if carried out in a sanatorium or hospital. The environmental conditions would certainly be less like those of a normal life.

The following table includes only cases of primary neurasthenia, and only those patients who have been discharged two years or over, and whose records are complete to date. Secondary neurasthenia, cases complicated by alcoholism, arteriosclerosis, tuberculosis, or other organic diseases, are omitted, as are also hysteria and the neurasthenia-like prodromal stages common to some of the organic psychoses.

It has proved difficult to obtain news from ex-patients (especially those who have been happily cured seem to be the slowest to answer our inquiries), and I have still to hear from some hundred or more.

Results of Treatment.

Of the 355 patients discharged two years ago or longer, whose records were complete at discharge, we know the present condition of 129. The following statistics of results apply, of course, only to this smaller number.

The standard by which the results are measured is as follows:

Improved means any distinct diminution of symptoms coupled with distinct increase in ability to live normally.

Much improved means ability to live a normal life and disappearance of at least 50% of the symptoms.

Cure means full ability to live a normal life without reappearance of symptoms and, if any emergencies and difficulties have arisen, ability to meet these in a normal way.

The statistics apply to the present condition of patients.

Patients discharged two years and over, 129.

No improvement	0.7%	
Improved	15%	
Much improved	36%	83%
Cured	47%	

Patients discharged three years and over, 91.

No improvement	1%	
Improved	11%	
Much improved	30%	87%
Cured	57%	

The higher percentage of cure in relation to "much improved," shown in the group of cases discharged longest, is suggestive of permanency in the results.

Duration of Treatment.

Average ..... 4 weeks (aggregate).
Longest ..... 6 months (aggregate).
40% treated for 1 week or less.

DISCUSSION.

Dr. Barker: Nothing could be more interesting than to hear a man like Dr. Riggs, who has seen so many neurasthenic patients, talk about his own first-hand experience with them. I was glad to hear him speak of neurasthenic states as abnormal mental states, for I think all of us who have studied them carefully feel that the most striking features of the complaints of neurasthenics are of a psychiatric nature. Indeed, I think that much of the progress that is being made in the understanding of the nature of neurasthenia, and in its treatment, is due to the rapid development of psychology and of psychiatry. Of course, those of us who have nervous patients sent to us—"complete-nervous-breakdown" cases—realize very well that what is called "neurasthenia" is no unity. We receive under this label a great many different kinds of cases, and it is only by a very careful analysis of each case that we can come to a correct understanding of its nature. We find that many "neurasthenics" are really patients with beginning dementia paralytica; some are instances of beginning dementia præcox; a good many more belong in the manic-depressive group; and a large number of them represent beginning Graves' disease. I might enumerate a number of other conditions that we quickly learn to differentiate and to recognize. All of these patients may present symptoms that are usually called "neurasthenic symptoms."

The study of these patients, and especially of their inability to adapt themselves to their environment, demands, as Dr. Riggs has said, a knowledge of psychology and, especially, of personality. I think that we can learn much from the comparative psychologists, particularly as regards the fundamental instincts. I do not believe that personality can be adequately understood without a thorough knowledge of the instincts. We must take into account the instinct of flight with its emotion of fear, the instinct of

pugnacity with its emotion of anger, the parental instinct with the tender emotion that accompanies it, the reproductive instinct with its accompanying emotions, the instinct of repulsion and its emotion of disgust, the instinct of curiosity and its emotion of wonder, the instinct of self-abasement with its emotion of subjection, the instinct of self-assertion with its emotion of elation, etc. We must realize that each one of these instincts has a cognitive aspect, an affective aspect, and a conative aspect; out of these instincts, as elaborated, is compounded our whole psychic life, our thinking, feeling and striving. In animals, we can see the instincts in their simpler forms; in man, we can see how, on the top of the instincts, are built up sentiments, that is, groups of ideas, feelings, and strivings, in which a series of instincts may be combined into a larger unit and directed toward some object outside, as when one loves or hates a person or a country. Especially important is the growth of the self-regarding sentiment and its relation to "moral conduct." This self-regarding sentiment helps us to understand the influence of the social environment upon a developing personality—the effects of rewards and punishments, and of approval and disapproval. Finally, we are beginning to understand how some men rise to "a plane of conduct higher than that regulated by the approval and disapproval of their social circle," where they may at times stand up against public opinion and do what they believe to be right in defiance of it. Only after we understand how personalities are built up can we hope to understand the maladies of adjustment met with in the psychoneuroses. Our newer knowledge regarding the instincts and sentiments we owe especially to the comparative, the behavioristic, and the social psychologists, to men like Lloyd Morgan, Stout, Shand and MacDougall. The book by MacDougall on Social Psychology has interested me enormously, and I can recommend it heartily to you for summer reading if you are not already familiar with it.

Dr. Riggs has spoken of Freud's ideas both favorably and unfavorably; and we like that kind of critical comment here. I feel as he does, that there is much that is good in Freud's method of psychoanalysis; it is often valuable, especially in extending the anamnesis. It seems to me that Freud has made a mistake in regarding as sexual in nature some emotions that comparative psychologists have shown us are not sexual emotions. For instance, I think Freud confuses the "tender emotion" of the parental instinct with the emotion of the sexual instinct. They are certainly sharply separable from one another, though in the sentiment of love of one person for another of the opposite sex, both of these emotions, along with others, may be concerned.

As to treatment by re-education, I concur in Dr. Riggs' view, that it is the best method of mental treatment we have for these patients. One must realize that the symptoms of the neurasthenic are not imaginary; their sufferings are real. They are just as real as those in typhoid or in measles. Sometimes the torture of these psychoneurotic states is as hard to bear as any physical pain to which people are ever subjected.

As to saying that neurasthenia is entirely mental in nature and origin, or that there is no physical basis for it, that takes one into rather deeper waters of discussion than I wish to enter just now. I, personally, believe that all the instincts have a physical basis, and that, in the building up of sentiments out of instincts, we have to think of the underlying physical or neural basis; and that this neural basis can be profoundly modified by environmental influences.

Dr. Riggs' paper touches upon many exceedingly interesting problems that might well be discussed, and I trust that others who follow me in the discussion will comment upon some of them.

THE GASTRO-INTESTINAL FINDINGS IN A CASE OF SPRUE, WITH A NOTE ON THE TREATMENT BASED ON THESE FINDINGS.

By THOMAS R. BROWN, M. D., Baltimore, Md.

The opportunities for studying sprue in this country are so rare that it seems justifiable to call attention to a case recently under our care, especially as intensive gastro-intestinal studies were made, from which certain conclusions of real interest could be drawn. Our work was entirely confined to observations in the digestive field, and did not touch upon what is perhaps the most interesting phase of the subject—the question of etiology. In this connection a great deal of work has been done in recent years, most observers concluding that the disease is parasitic in nature, as was originally suggested, I believe, by Galloway. Castellani at various times regarded a bacillus, a spirochæte, and many yeasts, respectively, as causative factors, finally concluding that the condition was due to a yeast infection—106 of the 112 strains isolated by him being *Monilia*—and this is certainly the latest and probably the best view held as to the origin of sprue, although Justi and Beneke still hold that the cause is a rod-like bacillus with its primary seat in the intestine, the epithelium of the villi being especially involved. Ashford, who believes that the yeast—Monilia—is the cause, thinks that this fungus is found primarily in the mouth. Bahr,[1] after making very extensive researches on this subject, comes to the following conclusions:

1. Sprue is a specific disease of tropical and subtropical countries, though it is possible that cases originate in temperate zones.

2. It is a disease prevalent in Ceylon, especially amongst the Europeans, but, contrary to the opinion hitherto held, it may also occur in the native, irrespective of race or mode of life.

3. This fact, together with the occurrence of the disease in people closely associated, suggests a local influence or some communication from man to man.

4. Sprue is a variable disease; it may occur in a mild or in a particularly virulent form; and in common with many other serious diseases, it is sometimes liable to sudden remissions and latent periods.

5. There is evidence that the disease may occur in distinct and specific clinical forms, according to the portion of the alimentary canal attacked.

6. Researches on the composition of the stools point either to a complete absence or to an inefficiency of the intestinal digestive ferments.

7. Researches on the blood and urine are in favor of regarding sprue as an alimentary toxæmia.

8. The pathological findings are also in favor of this supposition and point to an infection with the thrush fungus (*Monilia albicans*) as being the organism concerned in its production; the balance of evidence I have collected on the whole would seem to be in favor of, rather than opposed to, this view.

Incidentally, all attempts to convey the disease in its clinical entity to animals, even monkeys, have failed, although Ash-

[1] Trans. Soc. Trop. Med., 1913, VII.

ford's experiments[2] in this connection are extremely suggestive. Some of his conclusions are:

1. The species of Monilia recovered by me from now nearly one hundred cases of sprue, and apparently a new species from careful cultural and morphological investigations, is a pathogen for current laboratory animals by hypodermic inoculation.

2. This species, which I will for the present call Monilia X, is ordinarily a low virulence organism.

3. When recovered from a patient with sprue and promptly injected into certain laboratory animals, it generally produces their rapid death from a mycotic septicemia.

4. When grown for a long time and frequently transplanted, the same organism which rapidly killed soon after isolation from a sprue patient seems to partially or completely lose its virulence.

5. This virulence may be recovered by passage through susceptible animals, and even reach such a point as to sicken or kill these animals by continued feeding.

6. Ordinarily an animal may not be killed by feeding Monilia X when first isolated from a sprue patient. Its virulence must be augmented by passage before uniform pathogenicity through feeding can be demonstrated.

7. In such animals the symptoms depend on the part of the intestinal tube most affected, in the portion in which these Monilia secure their first foothold.

8. A certain number of animals exposed by feeding, rapidly die of a Monilia septicemia believed by me to be due to a sudden primary pneumonia and secondary septicemia.

9. Animals escaping this fate succumb more slowly to what seems to be a toxin developed in the intestinal tract by a localization of these Monilia.

10. Feeding experiments have resulted in the production of a stomatitis on two occasions and in the appearance of severe and long-continued diarrhœa on several occasions.

11. In one guinea-pig presenting a severe stomatitis, sections of the affected zone revealed Monilia in the midst of the muscular bundles below the subepithelial connective tissue. This may explain the tendency for sprue to recur after an apparent dietetic cure: the yeasts are starved out in the surface; the patient apparently recovers, and, later, the deep-lying roots of the mycelial layer push out toward the surface and re-establish a surface growth with its consequences and a relapse.

Our case occurred in a young woman of 24, married, with an absolutely negative family history and past history, and a normal digestive history except a tendency to constipation. She had lived in Porto Rico from March 13 to July 21, 1913, and from April, 1913, until the time she first came under our observation (July 20, 1914), had had a persistent diarrhœa—from three to twelve stools daily, associated with an extremely bad taste in the mouth, very suggestive of rotten eggs, and always worse when the diarrhœa was most marked, the stools being large, gray, and soft. On account of these gray stools, which had evidently been wrongly interpreted as evidence of gall-bladder disease, a cholecystostomy and incidentally an appendectomy had been done without any effect whatever upon the symptoms. While in Porto Rico the patient had drunk only boiled rain water, but had bathed in both salt and fresh water; she had had an eruption on her forearm suggesting mosquito bites, and had numerous ulcers in the mouth, especially on the lips. The case was definitely diagnosed as sprue, both in Porto Rico and in this country, by military physicians conversant with the disease, and in the presence of her symptom-complex it seemed hard to arrive at any other diagnosis. When first seen by us she presented the picture of extreme emaciation, weighing less than 70 pounds, and giving a history of having lost 35 pounds during her illness. The thyroid, eyes, tonsils, teeth, heart and lungs were normal; the abdomen was negative except for a slight splanchnoptosis; the pelvic organs were normal. The urine never showed anything pathological, and the Cammidge reaction was negative—the usual finding in sprue. The blood showed, R. B. C., 3,528,000; Hgb., 72%; W. B. C., 6200, with 56% of polymorphonuclear neutrophiles, 31% of small and 11% of large mononuclears, and 1.5% of eosinophiles. During her month's stay in the hospital the temperature was never above 99° F.; the pulse rate varied from 70 to 94. The stools were very characteristic; they were of large size, soft, fermenting, gray or yellow-brown in color, but not especially foul, usually of acid reaction, and containing some undigested meat, starch, and fat, but no pus, blood, amœbæ, ova, or parasites. The sigmoidoscopic examination was negative. On admission the gastric contents showed a complete absence of hydrochloric acid, with a marked diminution of pepsin. The quantitative estimation of the pancreatic ferment, by the method described by us elsewhere,[3] showed a complete absence of diastase, the ferment most satisfactorily studied, and also of trypsin and lipase, as far as we could determine. This absence of pancreatic ferments has been noted before in cases of sprue.

The treatment of the patient consisted in absolute rest, unlimited fresh air, oil rubs, a diet at first consisting exclusively of buttermilk, increased rapidly up to eight ounces every two hours, zwieback, dry toast, and other simple food articles being gradually added, until after about six weeks the patient was on a fairly general mixed dietary, including the simple meats, green and starchy vegetables, the former in purée form, stewed fruits, fruit juices, butter and cream. Medicinally, she was given dilute hydrochloric acid and large doses of pancreatin—30 grains daily, together with calcium carbonate and a little tannic acid. We did not use emetin, as suggested by Schmitler. The patient improved very rapidly as regards weight, strength, and symptoms, the diarrhœa practically disappearing after a few days of treatment. When seen again in about four months' time she had gained a little over 20 pounds. The gastric contents then showed a small amount of free hydrochloric acid, but examination of the stools still showed a complete absence of the pancreatic ferments. When seen again, after another four months, she had gained altogether 35 pounds—in other words, her weight had become normal. She seemed absolutely well, had no digestive symptoms, and was on a general mixed dietary, the only foods she was unable to digest being corn, asparagus and oysters. The gastric analysis now showed normal amounts of hydrochloric acid and pepsin; incidentally, it may be said that the dosage of acid had been gradually reduced and finally discontinued without the appearance of any unpleasant symptoms. The stools,

[2] Am. Jour. Med. Sci., April, 1916, p. 520.

[3] Johns Hopkins Hospital Bulletin, July, 1914.

however, still showed a complete absence of pancreatic ferment, and the patient herself had noted that, although stopping the muriatic acid produced no unpleasant symptoms, whenever the pancreatin was omitted for a few days there would always be a return of the diarrhœa with the characteristic gray, frothy stool. The patient was heard from very recently and is absolutely well except for the fact that she still has to take the pancreatin in order to prevent a return of the diarrhœa.

The diagnosis seems quite definite. Two of the diseases with which sprue is sometimes confused—pernicious anæmia and atrophy of the gastric mucosa—can certainly be eliminated, while too long a time—almost two years—has elapsed and the condition of the patient is far too good to warrant a suspicion of malignant disease of the pancreas.

This persistence of the pancreatic achylia is of sufficient interest to warrant the reporting of this case, and suggests that, whatever the primary cause of the disease may be, certainly the appreciation of its effect upon the pancreatic secretion is of the utmost importance in the proper interpretation of the symptoms and signs in this disease.

The most striking features in our case were, first, the persistence of the complete absence of pancreatic secretions, not only during the stage of apparent illness, but even after the patient felt and seemed absolutely well; second, the essential rôle of the constant administration of pancreatin by mouth in the therapy of the disease; third, that whatever the cause of sprue, and at this writing it seems probable that it is due to an infection with monilia, the lack of pancreatic secretion seems persistent and fundamental, the absence of gastric juice variable and accidental; fourth, that as long as our patient still suffers from this pancreatic achylia she can in no wise be considered as cured, although clinically she is apparently well; and the ultimate outcome must still remain doubtful.

A UNIQUE CASE OF ATROPHY OF THE FATTY LAYER OF THE SKIN, PRECEDED BY THE INGESTION OF THE FAT BY LARGE PHAGOCYTIC CELLS—MACROPHAGES.[1]

By T. C. Gilchrist, M. D., and L. W. Ketron, M. D.

(From the Dermatological Department of The Johns Hopkins University.)

The patient was a young girl, aged 8 years, who came of a good family. There was nothing of importance in the family history. She was a seven months' child, but there were no complications at birth.

In April, 1915, six months previous to our first examination, the mother had noticed a spot on the calf of the right leg. This was soon followed by lesions on the other leg and later on the thighs. The mother described them as "lumps under the skin which appeared to the naked eye as dimples." During this period of the development of the disease the patient's health was not very good. She had feverish attacks and loss of appetite on several occasions. There were no definite subjective symptoms. Various therapeutic measures were tried, but without any favorable results on the course of the disease.

Examination.—The patient was a rather underdeveloped, moderately nourished child, weighing 37 pounds. She was bright, rather serious-minded, and the expression on her face was that of a much older child.

The cutaneous changes were present only on the lower extremities, extending from the inguinal region to the ankles (Figs. 1 and 2).[2] The anterior and outer surfaces of the thighs were comparatively free, the condition being limited to the inner and posterior aspects. The greater portion of the legs was implicated except over the knees and directly over the anterior tibial surfaces. The most striking thing noted on general inspection was the distorted contour of the legs, visible even with the stockings on, due to areas which were apparently sunken below the normal level of the skin.

Thighs.—The smallest lesion which could be seen was a pea-sized, irregular or round, bluish-tinted, slightly depressed macule, which was not sharply defined, but faded out gradually into the surrounding tissue. From these were formed larger, sunken, morphœa-like patches, which were round, irregular or band-like, and attained to an area the size of 10 x 4 cm. The depth of the atrophy varied from something scarcely perceptible in the smaller lesions, to about 2 mm. in the larger ones. The skin over the atrophic areas looked entirely normal except for a dusky bluish color, which became more pronounced as the lesions increased in size. The edges were not raised above the normal level of the skin and arose from the atrophic center gradually or rather abruptly. There was no redness or scaling of the lesions.

On palpation of the affected area a new condition was found which was not manifest to the naked eye. This consisted of hard, sclerotic, freely movable, irregular or branching masses or strands, which varied in size from some which were barely palpable to others as large as a man's finger. These masses lay in the subcutaneous tissue and ran beneath the smaller atrophic macules and the apparently normal skin. They did not invade the tissues beneath the larger patches where the atrophy was complete, but in some cases were continuous with the edges of these patches. These subcutaneous strands extended for the most part down the inner sides of the thighs. The skin over the larger atrophic patches gave the normal elastic sensation. It was not hardened, was freely movable, and could be picked up between the fingers in the same manner

[1] To appear simultaneously in The Journal of Cutaneous Diseases, October, 1916.

[2] We wish to express our thanks to Mr. Martin, of the Phipps Clinic, for his care in making our photographs.

as the normal skin over portions of the body where there is little or no fatty layer. The skin over the smaller macules could not be picked up in this manner, but was bound down, in many cases, to one of the deep infiltrations, giving a sensation similar to that found on palpation of a schirrous cancer of the breast. The edges of the large lesions were soft and usually passed abruptly into the normal skin; or, in some cases, they could be felt to be continuous with the subcutaneous infiltrations. At the edge of one of the atrophic patches two or three finger-nail-sized flat lumps could be felt, which had a cartilaginous hardness.

Legs.—On the legs the atrophic process had involved the greater portion of the posterior and lateral aspects. Here were seen palm-sized atrophic areas which spread with a smooth or serpiginous border. These had become confluent with other patches, leaving here and there islands or tongues of normal-looking tissue which felt hard or œdematous. The lesions on the legs differed from those on the thighs, in that they had indurated, pinkish-yellow or reddish edges which were covered by a few thin white scales. The skin over these lesions was elastic and was not bound down. It had a dusky bluish color, and beneath it the veins were distinctly visible. On the legs the subcutaneous infiltrations were not so distinct, because almost all the normal-looking tissue in this region felt like a brawny œdema or, in some cases, almost sclerodermatous tissue. There was some œdema with pitting at the lower border of the atrophy about the ankles. A slight elevation of temperature over the reddish edges of the lesions of the legs was perceptible.

Histological Examination.—Two pieces of tissue were excised for histological study and stained with the usual stains.

Preparation 1.—This tissue represented the smallest nodule which could be detected on the patient's thigh on deep palpation. Its existence gave no visible signs on the surface of the skin. It was hard to the touch and appeared to lie beneath the cutis.

The changes in the section were confined entirely to the fatty layer. The epidermis and the corium were unaffected. In the upper half of the fatty layer a small cellular nodule was seen, which was divided into lobules by the connective-tissue strands that passed down perpendicularly from the lower portion of the cutis (Fig. 3). This cellular infiltration, towards its center, had replaced most of the fatty tissue, but towards the periphery the fat spaces became more numerous and the infiltration gradually ended with prolongations, or isolated groups of cells, which lay between the strands of the fat framework. The new growth, towards the center, consisted of a cellular connective tissue within which numbers of plasma cells were scattered diffusely or lay in groups (Fig. 5). Towards the periphery, where numbers of fat spaces still remained, the infiltration was made up of fibroblasts, large endothelioid cells, small round cells, and scattered here and there, rather thickly in some areas, plasma cells and a few polymorphonuclear leucocytes. Besides these, there were other numerous and striking cells which were markedly conspicuous because of their arrangement and abundant protoplasm. These lay mostly in the fat spaces, in some cases filling them; in others, lining them with gland-like regularity (Figs. 8 and 9). They were found mostly in the depths of the infiltration, but in the earliest stages of their formation isolated groups lying near blood vessels were occasionally seen at the extreme edge of the infiltration (Fig. 4). The nuclei of most of these cells were large, oval, irregular, or round, with a heavily staining chromatin network (Figs. 8 and 9). Some of them, however, were small, with a picnotic appearance, while others were larger, with a more faintly staining chromatin network. Mitotic figures were occasionally seen. The cells usually contained from one to three nuclei, but large giant cells were found with 50 or more nuclei (Fig. 6). The protoplasm was frequently two or three times the width of the nuclei, stained faintly with eosin and polychrome methylene-blue, and appeared as a fine foam-like network (Fig. 9). The contour of the cells varied with their location. When they completely filled the fat spaces, they were irregular or had a mosaic-like arrangement. If they surrounded the fat space, they were usually rectangular in shape, resembling the flattened cuboidal epithelium of a glandular structure (Figs. 8 and 9). In rare instances the fat spaces were surrounded by cells which did not have this foam-like protoplasm and suggested a cell of a leucocytic type (Fig. 4(*b*)).

In the comparatively normal fatty tissue surrounding the infiltration here and there could be seen small dilated blood vessels containing a number of polymorphonuclear leucocytes. Some of these vessels showed a proliferation of their endothelial lining and of the connective tissue surrounding them. Lying between the strands of the non-infiltrated fatty framework small groups of epithelioid or fibroblastic cells or plasma cells were occasionally seen.

Preparation 2.—This piece of tissue was excised from one of the large patches on the leg extending from the atrophic center through the elevated pinkish edge (Fig. 7). Here the changes were seen principally in the subcutaneous tissues. There was a slight scaling of the horny layer of the epidermis and a mild infiltration about the blood vessels in the cutis of the left half of the section. In the left third of the section (*A*), which corresponds to the elevated edge of the lesion, an infiltration was found in the fatty layer similar to that found in Preparation 1 (Fig. 7 (*d*)). In following the section towards the right, the fatty tissue was seen to give way rather abruptly to a dense sclerotic tissue (*B*), within which were found, in nests or more or less diffusely scattered, large fibroblastic cells, large and small round cells and plasma cells. Newly forming and thickened blood vessels, showing endothelial proliferation, were seen. One small inclusion of fatty tissue was found, in which were seen the large cells described above (Fig. 10). Further towards the right, in an area corresponding to the atrophic center of the lesion, the sclerotic tissue became less prominent and very few changes were noted except the entire disappearance of the fatty layer (Fig. 7 (*c*)).

A polychrome methylene-blue stain of both preparations showed no unusual increase of the mast cells. No change in the elastic tissue of the cutis was noted.

FIG. 1A.—Photograph, front view.

FIG. 1B.—Photograph, back view.

FIG. 2.—Photograph of a painting of the inner portion of the thigh and leg, by Prof. Max Broedel.

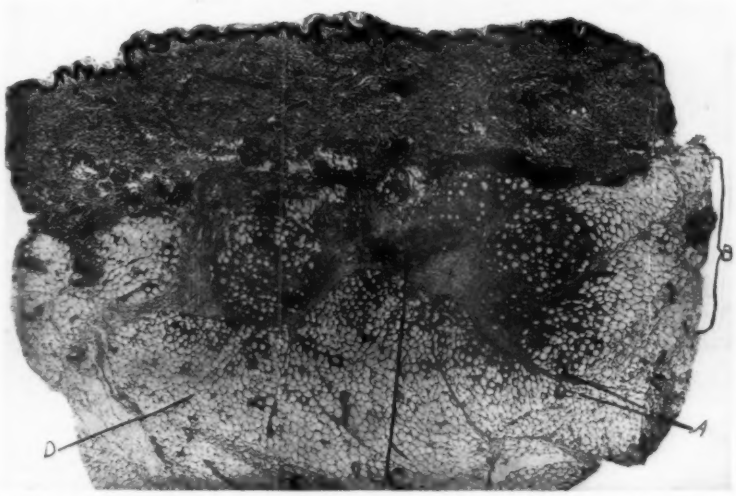

FIG. 3.—This represents the smallest lesion which could be palpated on the patient's thigh. The cellular infiltration is seen lying in the fatty layer *B* beneath a normal cutis. *A* is magnified in Fig. 4. *C* is magnified in Fig. 5. *D*, practically normal fat.

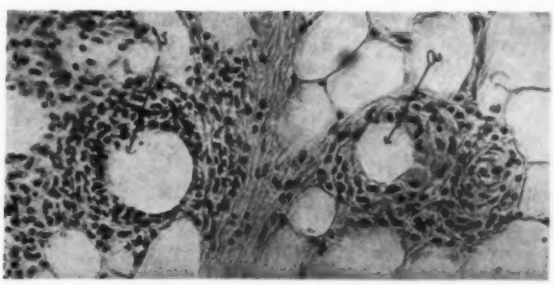

FIG. 4.—(Magnified portion *A* in Fig. 3.) At *a* is seen one of the earliest changes in the growth of the lesion seen in Fig. 3. Here is a small group of macrophages lying by the side of a blood vessel which is surrounded by normal-looking fatty tissue. At *b* is seen a fat globule surrounded by cells of a leucocytic type.

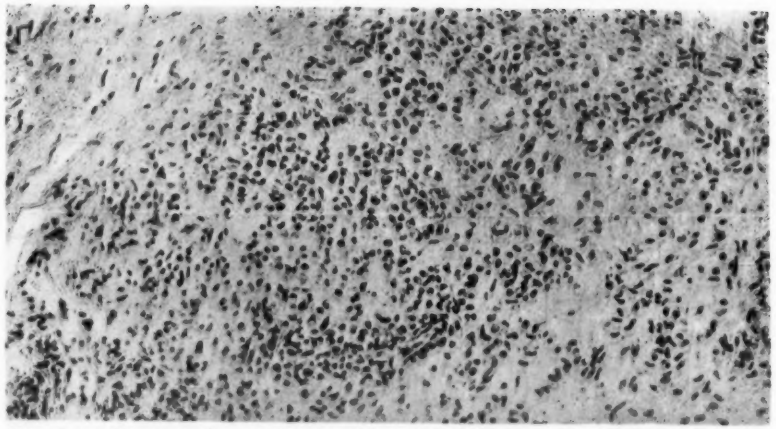

FIG. 5.—A large number of plasma cells, which were found towards the center of the infiltration shown in Fig. 3. (Magnified portion *C* in Fig. 3.)

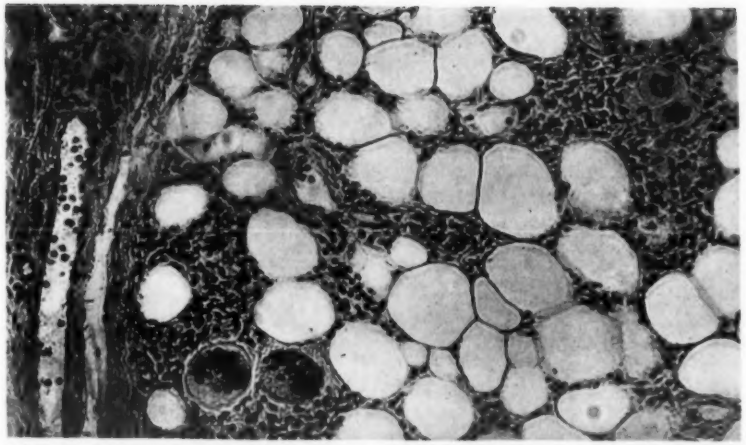

FIG. 6.—This section shows the large giant cells which are formed by the confluence of the macrophages.

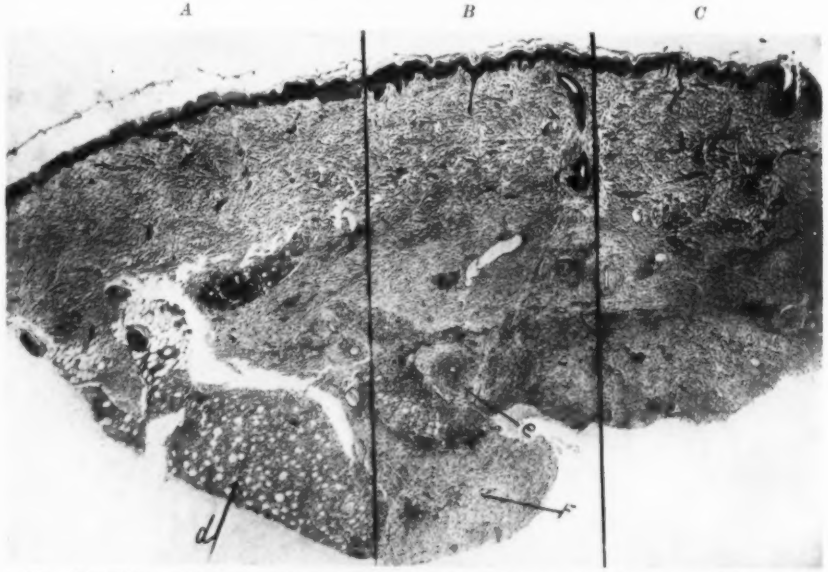

FIG. 7.—This section was taken through the edge of one of the large atrophic patches on the patient's leg. *A* represents the normal-looking, although slightly reddened, skin and shows the infiltration *d* in the fatty layer which is of a character similar to that seen in Fig. 3. *B* shows replacement of the infiltration in the fatty layer by sclerotic tissue. *C* represents the atrophic area in which the skin is practically normal except for the absence of the fatty layer. (*d* is magnified in Fig. 8; *e* in Fig. 10 and *F* in Fig. 11.)

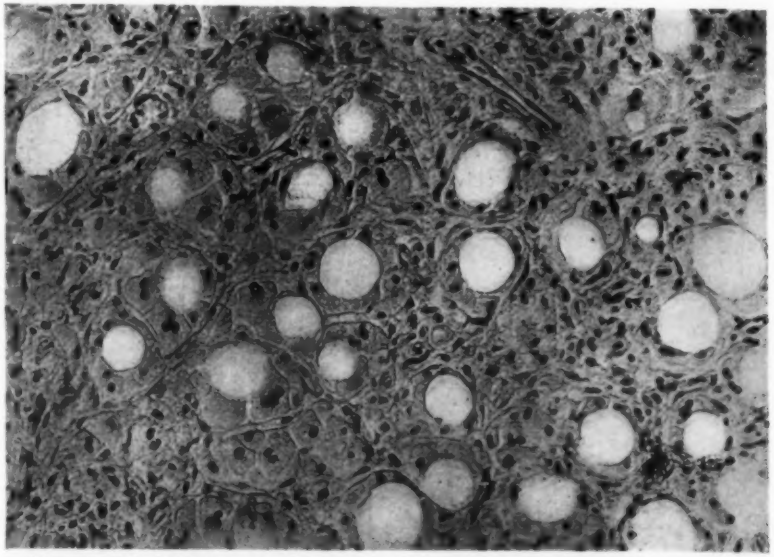

FIG. 8.—(Magnified portion *d* in Fig. 7.) Here is seen the arrangement of the large macrophages which fill the fat spaces or surround them with gland-like regularity.

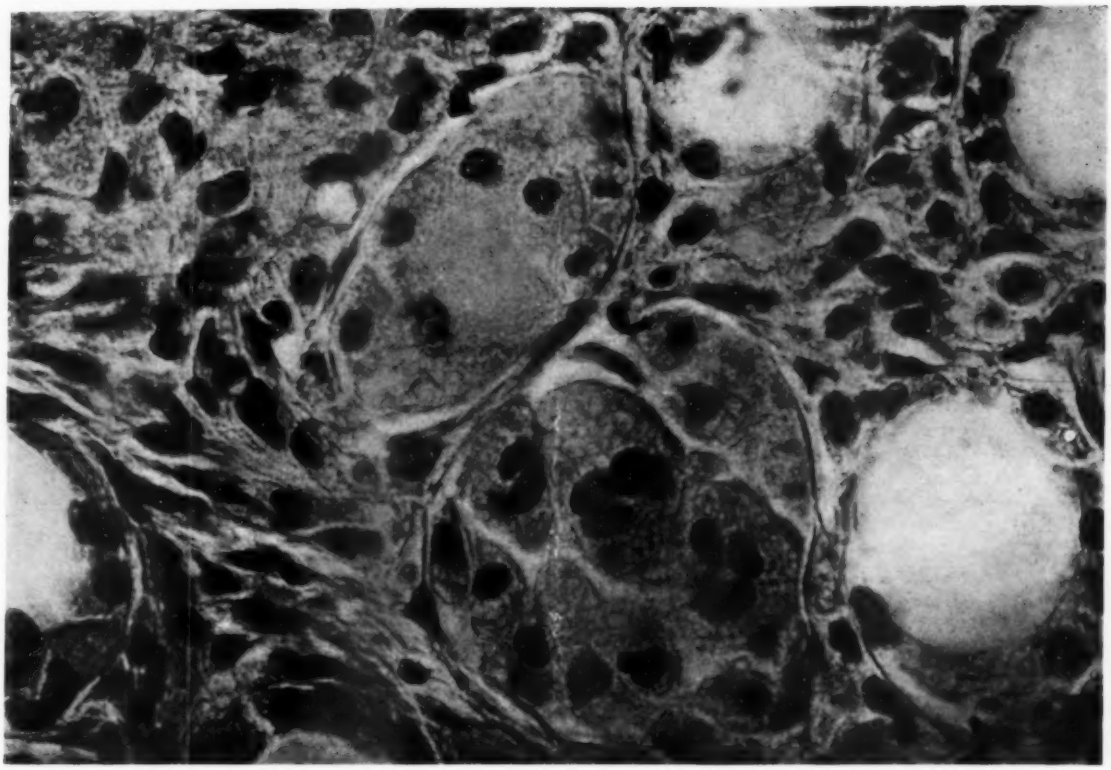

FIG. 9.—A high magnification of the macrophages showing their foam-like protoplasm. In the lower right-hand corner they are seen surrounding a fat space. Immediately to the left of this area they have completely filled the fat space.

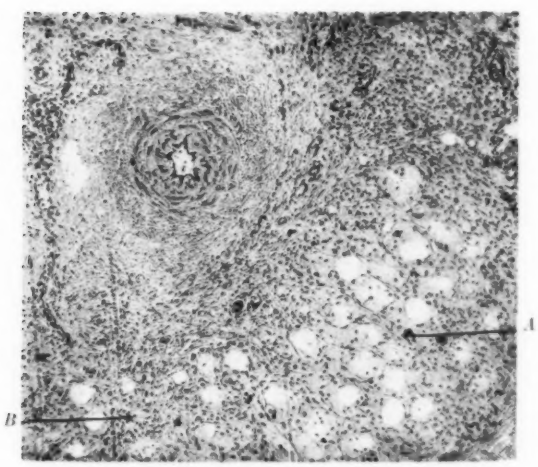

FIG. 10.—(Enlargement of Fig. 7, at *e*.) A small inclusion of fatty tissue surrounded by a richly cellular connective tissue. A degeneration of the tissue surrounding the artery is to be seen. Transition changes present from *A* to *B*.

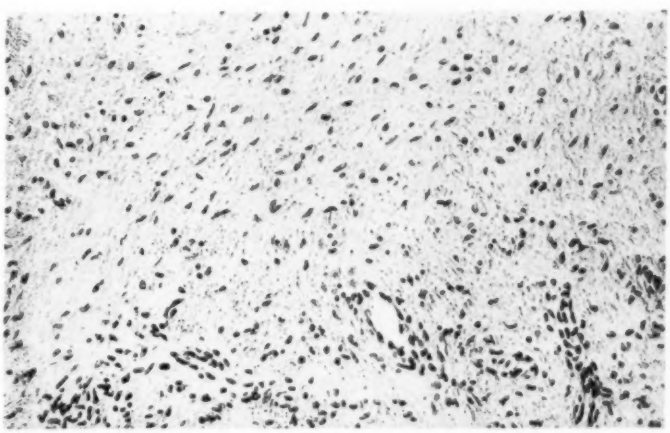

FIG. 11.—Sclerotic tissue which has replaced the fatty layer, representing a stage later than that shown in Fig. 5. (Magnified portion *F* in Fig. 7.)

In order to study the fatty tissue of these preparations, some of the fresh tissue was stained with Soudan III. The fat spaces were seen to be filled with large, red-stained fat globules. The large single or multinucleated cells already described, which surrounded or replaced a fat globule, were filled with reddish-staining granules. These granules were also occasionally found in the cells lying in the infiltration at some distance from the fat.

The resemblance of these large cells to xanthoma cells, and the fact that the granules which they contained were shown by the Soudan III stain to be of a lipoid nature, led also to investigations to determine the presence of cholesterin. Dr. Shipley, of the Anatomical Department, tested some of the fresh tissue with the polariscope, but no doubly refractive substances were found.

General Observations while the Patient Was in the Hospital.—The patient was admitted to the Harriet Lane Home (Johns Hopkins Hospital) on October 28, 1915, about seven months after the beginning of the disease, and remained there during a period of about two months. Dr. Howland and other members of the hospital staff examined the patient, but nothing definitely pathological could be found with the exception of the skin lesions. Dr. C. M. Byrnes, who referred the case to one of us, found no abnormalities in the nervous system. There were no muscular disturbances and the glands of internal secretion were normal, as far as could be determined.

The Wassermann and von Pirquet reactions were negative. The urine contained no albumin, sugar or casts.

Dr. Shohle made a determination of the cholesterin of the patient's blood, but found no increase above the normal limits. (He examined at the same time the blood of a patient who showed numerous xanthoma lesions on the buttocks and elbows, and found a considerable increase in the cholesterin content.)

The temperature of the patient, which was 101° F. on entrance to the hospital, was subject to slight elevations at various times, but with no regularity. The white blood-cell count was 15,600, and the increase was in the polymorphonuclear elements.

From the time of admission the patient was about the ward and outside daily, except during the two attacks described below. She had a very good appetite and only complained, at various times, of indefinite pains in the legs. No internal medication was tried except potassium iodid, which was given for only a few days without benefit.

On December 9, about six weeks after admittance to the hospital, she had an acute attack of toxic erythema with macules and papules scattered over the body. This followed a period of constipation, and lasted three days. On December 17 she had a second attack of a toxic rash, associated with a rise in temperature and swelling of the joints. During this time the white blood-cell count was 26,000; a differential count showed, P. M. N., 86%; P. M. E., 1.6%; S. M., 8%; L. M., 1.2%; Trans., 3.2%; Hgb. (Sahli), 70%. This attack lasted also about three days, at the end of which time she was able to be up and about the ward.

On December 21 the patient was taken home with no definite change in the skin condition. She had gained two pounds in weight.

General Discussion.—The clinical course of the disease while the patient was in the hospital gave very little assistance as to the nature of the condition except that the slight, irregular rises in temperature, associated with the high leucocyte count, were suggestive of some chronic inflammatory process with suspicious exacerbations. The attacks of toxic erythema, we feel, might have had some connection with the course of the disease.

The histological findings show that the lesions in their development and evolution follow a definite course, which leads to the ultimate loss of the fatty layer without other permanent changes in the skin. The disease begins with the formation in the fatty layer of small nodules or strands, which are not perceptible to the naked eye, but are recognized only on deep palpation. These small nodules are made up of cells of a chronic inflammatory nature. The inflammatory process spreads only in the fatty layer, the fat itself being taken up in the cytoplasm of large phagocytic cells, which are very striking in appearance. After the fat has been removed the infiltration gives place to a fibrous tissue, the contraction of which leads to the formation of the small atrophic macules visible on the skin and which are bound down to the underlying masses. Later, as the lesions increase in size, this fibrous tissue is itself absorbed, leaving a soft, elastic skin which, owing to the loss of the fatty layer, has sunken down directly upon the muscular fascia. Since the edges of some of the lesions showed no induration, the sunken areas rising directly into the normal-feeling skin, the process must be subject to spontaneous arrest. The fact that the areas affected return to a practically normal state, except that the fatty layer is entirely lost, furnishes strong presumptive evidence that the rôle of the pathological process is to remove the fatty layer. This assumption is best supported if we further assume that the fat itself, through some chemical change, has been converted into a substance still of a fatty nature, but which acts as a foreign body in the tissues. The other possibility is to assume that the condition is an infective process, and that the invading organism has a special affinity for the fatty layer, changing the fat into some substance which acts as a foreign body. The difficulty here is that, if bacterial in origin, one would not expect the process to be so narrowly confined to the fatty layer and, also, would not look for such complete restitution of the areas affected after removal of the fat.

As to the nature of these phagocytic cells, they no doubt belong to what is classed as the "macrophage" group. This term, which was introduced by Metchnikoff, was at first rather indefinite in its application, but lately, especially as the result of the work of Evans[1] with the acid azo dyes, it is now applied to a definite and important group of cells. When animals, which are normal or have been experimentally infected, are

[1] Evans: "The Macrophages of Mammals." Amer. Jour. of Phys., 1915, XXXVI.

injected intravenously with these azo dyes, *e. g.*, trypan blue, the dye is stored in various portions of the body in the cytoplasm of certain large mononuclear cells, which have the power of taking up finely particulate matter. To this class of cells belong the Kupffer cells of the liver, which in malarial infections are filled with pigment, and the cells of the bronchial lymph glands, which in anthracosis contain pigment particles (coal dust). Other cells of endothelial origin, according to Evans, which have the power of taking up foreign bodies and which are found in the spleen, bone-marrow and the serous cavities, belong to this special group, as do, also, the clasmatocytes of the skin and the foreign-body giant cells. It has been shown by Evans, Winternitz and Bowman[4] that the epithelioid cells and the giant cells of the miliary tubercle are pure colonies of these macrophages.

The similarity of the macrophages occurring in our case to xanthoma cells is striking. Anitschow[5] has shown, in the experimental production of xanthoma by introducing foreign bodies into the skin of animals fed on cholesterin, that large macrophages are first called forth by the introduction of the foreign bodies, and these are later transformed into the typical xanthoma cells because they take up the extravasated cholesterin which is present in excess in the blood. In xanthoma the foreign material is in the blood as a cholesterol-fatty-acid-ester, while in our case the foreign material is probably formed *in situ* from the normal fat.

In conclusion, we may say that, in the condition which we have described, there is a gradual progressive change in the fat of the subcutaneous tissue of the skin, due to some unknown cause. This metamorphosed fat now acts as a foreign body in the tissues and calls forth a foreign-body inflammatory reaction. Macrophages, derived from the resting-tissue cells, the endothelium of the capillaries, and probably from the connective-tissue cells, now appear and phagocytose this changed fat, which they probably liberate in some soluble, inert form that can be excreted through the blood and lymph-channels.

After the fat has disappeared, this inflammatory reaction, its function accomplished, is replaced by a fibrous tissue which itself gradually disappears, leaving the skin practically normal with the exception of the absence of the fatty layer.

Note.—We saw the patient again in May, 1916, six months after our first observations. The changes observed were very interesting and corroborated and made stronger our previous convictions as to the nature of the pathological process. Two or three new depressions had appeared on the outside of the thighs, and those on the inner sides had increased in size. The atrophic process had practically covered the whole of the legs which now did not present the irregular contour observed at first, but looked and felt almost normal except for their extreme thinness, due to the absence of the fatty tissue. The induration, redness and œdema had disappeared, and the scar following the excision of our Preparation II, which was taken through the reddish, scaly, indurated edge of one of the large patches on the leg, was now surrounded by skin which on palpation gave a normal, elastic sensation. The mother said that the child had had another attack of a toxic rash, and at times still complained of pain in her ankles, but otherwise had been in very good health. There seemed, at this time, to be no interference with her muscular activity.

[4] Jour. Exper. Med., 1914, XIX.
[5] Arch. f. Dermat. u. Syph., 1914, CXX.

TETANUS FOLLOWING GUN-SHOT WOUNDS.

By J. A. C. Colston, M. D.

Tetanus, during the early part of the present European War, was a frequent and fatal complication, particularly of wounds caused by shell fragments. The prevalence of the infection was attributable to a number of environmental conditions, the most important of which was the highly fertilized soil of the northern and eastern departments of France, upon which the early sanguinary actions took place. In these regions practically all lacerated wounds were exposed to contamination with soil rich in tetanus bacilli and offered especially favorable conditions for their development. A further source of contamination lay in unsatisfactory transportation facilities. For example, some observers have claimed that the high percentage of tetanus infections among the French wounded, during the first month of the war, was due in no small part to the fact that many of these patients were carried, after being wounded, in cars which had been used for the transportation of horses and cattle to the fighting zone.

As soon as the prevalence of tetanus became evident, attention was called to the fact that practically none of the wounded at this time were given prophylactic doses of antitetanic serum, as this was impossible as a routine procedure on account of the limited supply on hand and the large number of casualties. The importance of this measure was emphasized by Tuffier,[1] who was commissioned by the French war office to inspect the medical service of the French army. In his report before the Academy of Medicine of Paris on October 13, 1914, he placed especial emphasis on the necessity of the routine injection of all wounded men with antitetanic serum. Coincidently with the introduction of this measure a remarkable reduction in the number of cases was noted.

Following the distribution of ample supplies of antitetanic serum by the French Sanitary Service to all dressing stations and receiving hospitals near the firing line, the wounded, practically without exception, received a prophylactic injection within 24 hours after injury, and a patient arriving at a base hospital without having had such an injection at present writing is a rarity. The isolated cases of tetanus that are still seen can almost all be explained by some omission or delay in the administration of the prophylactic dose.

Never before has the efficacy of antitetanic serum as a preventive of tetanus received proof on a larger scale, and when the records of the medical services of the belligerent armies become accessible, a comparison of the incidence of tetanus in the first two months of the war, when facilities for prophylactic injections were insufficient, with that in the succeeding months, when a thorough application of preventive inoculation was possible, will furnish the most certain proof of this simple and life-saving measure.

A considerable amount of literature dealing especially with the prevention and treatment of the great number of cases occurring during the early part of the war has already appeared. In addition to preventive inoculation, the importance of the early disinfection of the wound has been emphasized. Rogers,[2] in some experiments conducted in 1905 upon rats, had already demonstrated the importance of this measure. He introduced street dust into multiple incised wounds; and of six animals so treated four died with tetanus, while of the six control animals whose wounds were irrigated with potassium permanganate solution, none developed symptoms. Unfortunately, in the majority of cases of gun-shot wounds such a procedure is inapplicable on account of the deep penetration of fragments of projectile and bits of clothing.

Fleming, in some interesting cultural studies of severe wounds, has furnished experimental proof of the efficacy of preventive inoculation. In an extensive series of anaerobic cultures from unselected cases he found 11 in which tetanus bacilli were recovered from badly lacerated and infected wounds. All of these patients had received antitetanic serum soon after the wound had been inflicted, and in only two had symptoms of tetanus appeared, these being mild and followed by a prompt recovery.

For practical purposes, three distinct types of the disease may be recognized clinically, according to the length of the incubation period. The acute fulminating type with onset of symptoms within three or four days after the infliction of the injury almost invariably results fatally, and treatment must necessarily be limited almost entirely to the relief of the distressing spasms. These cases are usually seen in field or evacuation hospitals, but one typical case of this type was observed in our service:

CASE 1.—Charles X., aged 26, was brought to the Sacré Coeur Hospital at Pau, one of 100 more or less seriously wounded patients. All the others had received prophylactic injections of serum before being placed on the hospital trains. The patient had been struck in the left hand about 60 hours before admission by a shell fragment, which had caused a compound fracture of the third and fourth metacarpal bones, with extensive laceration of the soft parts. He had refused the routine prophylactic injection at the evacuation hospital. Twelve hours after admission cramp-like pains developed in the left arm, rapidly followed by trismus. The patient died 36 hours later, after a typical course of opisthotonos, general tetanic spasms and firmly locked jaw. Intramuscular injections of antitenanic serum had no apparent effect.

The second and most frequent type is that in which the incubation period varies from five to 14 days. The mortality is between 60% and 70%, but it would seem that this could be considerably reduced by an early recognition of the disease, prompt and thorough local measures and a careful choice of treatment. Five cases of this type were observed, four in the French Red Cross Hospital with three deaths, and one in the temporary hospital of the American Red Cross, treated with intraspinal injections of magnesium sulphate, with recovery.

CASE 2.—Alfred X., aged 40, was brought to the temporary hospital at the Palais d'Hiver on November 3, having been wounded 72 hours previously by shell fragments. He had received no antitetanic serum before admission, and none was given after his entrance, on account of the limited supply. Examination revealed an infected wound of entry on the posterior external aspect of the right buttock. There was no wound of exit. The roentgenograms showed a fragment of shell lying external to and about 5 cm. below the iliac crest. The wound did not drain well and signs of a localized infection developed, with a gradually rising temperature. On November 8, under chloroform anesthesia, the wound of entry was enlarged, an abscess evacuated and the projectile, with some fragments of clothing, removed. The wound was irrigated with salt solution and free drainage assured by means of a tube. The temperature promptly fell to normal and a satisfactory convalescence seemed assured.

On November 12, nine days after admission and 12 days after being wounded, the patient complained of cramp-like pains in the right leg and slight stiffness of the jaw. Ten cubic centimeters of antitetanic serum (Pasteur Institute) were injected intramuscularly. The next morning the stiffness of the jaw was more pronounced and tonic spasms of the leg were more frequent, with a general increased activity of the reflexes. The wound was opened widely, swabbed out with iodine and irrigated with potassium permanganate solution. No retention of pus was found. During the day three more intramuscular injections of serum were given, together with large doses of sodium bromide and chloral hydrate. During the next three days this treatment was continued, the patient receiving 30 cc. of the serum per day. The symptoms, however, became progressively worse and general tetanic convulsions and opisthotonos supervened. During the more severe spasms respiration ceased and cyanosis became pronounced. As these spasms were becoming more frequent and longer in duration, it was feared that a fatal result might occur at any time from spasm of the glottis. A lumbar puncture was done on November 16, chloroform being necessary to produce the necessary relaxation. Ten cubic centimeters of clear fluid under slight tension were withdrawn. Using the dosage of 1 cc. for each 25 pounds of body weight, as advised by Meltzer,[3] 6 cc. of a 25% magnesium-sulphate solution was slowly injected, the head being kept slightly elevated to avoid involvement of the respiratory center. The respiration immediately became slow, shallow and irregular, but at no time was artificial respiration necessary. No appreciable effect was noticed on the heart. Several hours after the injection the temperature rose to 104° F. The patient remained deeply unconscious and completely relaxed during the next 36 hours. At the expiration of this time slight general contractions again appeared, but severe general spasms were absent, and, as respiration was unimpeded, no further injection was deemed advisable. Catheterization and nasal feeding were necessary for six days following the injection. The patient slowly recovered consciousness, was later able to take food by mouth, and regained control of the bladder and intestine. No contractions were noticed after the fifth day following the injection, and by the seventh day the rigidity of the jaw had completely disappeared. Stiffness in the right leg remained, however, for about six weeks, and convalescence was delayed by a somewhat severe bronchitis.

This case is unusual, in that a severe type of the disease developed after a rather long incubation period. The com-

plete relaxation obtained after the intraspinal injection carried the patient over what was apparently the critical period of his illness.

CASE 3.—Prosper X. was admitted to the French Red Cross Hospital five days after receiving a compound comminuted fracture of the first two metatarsal bones of the right foot. He had received no preventive injection, and no serum was obtainable after his admission to the hospital. The wound was foul and was complicated by an ascending lymphangitis, involving the foot and the lower two-thirds of the leg, which was treated by hot applications. Under this treatment combined with daily irrigations of the wound, the infection was successfully controlled until six days after admission, when cramp-like pains in the right leg with rigidity of the jaw appeared; the incubation period being thus 11 days. The wound was swabbed out with carbolic acid, and large doses of chloral hydrate were administered. The disease made rapid progress and the patient died in a severe convulsion 72 hours after the first symptoms were noticed.

CASE 4.—Henri X. was admitted to the French Red Cross Hospital five days after receiving penetrating wounds of the left heel and left shoulder. No preventive injection had been administered. On the day after admission a piece of shell with some comminuted fragments of the os calcis were removed under chloroform, and the wound was irrigated with salt solution. The condition of the wound improved steadily until six days after admission (11 days after the injury), when cramp-like pains in the left leg with rigidity of the jaw appeared, soon followed by general tetanic spasms. The patient was given daily intramuscular injections of 20 cc. of a 3% carbolic-acid solution combined with large doses of chloral. This treatment seemed to have little effect on the progress of the disease, and the patient died in general tetanic spasms five days after the appearance of the symptoms. No antitetanic serum was available for the treatment of this case.

CASE 5.—Jean X. was admitted to the French Red Cross Hospital with a compound fracture of the right tibia of six days' duration. No preventive inoculation had been given. The wound was badly infected and an ascending lymphangitis appeared and spread rapidly. Three days after admission the wound was opened widely under chloroform, numerous fragments of comminuted bone were removed, the cavity was irrigated with salt solution, and the whole leg put up in a large, hot, wet dressing. Under this treatment the lymphangitis subsided and the patient seemed to be making satisfactory progress until three days later (11 days after the injury), when he began to complain of cramps in the right leg. Rigidity of the jaw appeared on the next day, followed by spasms which subsequently became general. Following the appearance of the first symptoms the patient received daily intramuscular injections of 20 cc. of a 3% carbolic-acid solution. No antitetanic serum was given. The disease progressed slowly; the spasms became gradually more severe until death supervened from exhaustion, 11 days after the onset of the first symptoms.

CASE 6.—Mohammed X. was admitted to the French Red Cross Hospital with a comminuted fracture of the third and fourth metatarsals of the left foot, inflicted five days previously. No preventive injection had been administered. There were no untoward symptoms until six days after admission (11 days after the injury), when painful tonic spasms of the leg and slight rigidity of the jaw were noticed. Antitetanic serum (10 cc.) was immediately given. The slight general spasms continuing, a modified Pirogoff amputation of the foot was done, and daily intramuscular injections of 12 cc. of a 3% carbolic-acid solution were administered. For five days following the operation the patient was very ill with generalized spasms, opisthotonos and extreme rigidity of the jaw. The symptoms then became gradually less severe and entirely disappeared on the twelfth day.

This series of cases is, of course, too small to demonstrate the value of any method of treatment. The most striking result was obtained in Case 2, with the intraspinal administration of magnesium sulphate. This method was first introduced after the experimental studies of Meltzer and Auer. Blake[6] reported two cases in which the procedure was used successfully. Miller[8] reported another successful case and added a review of all cases treated by the method up to 1908. Falk[9] reported favorable results in cases occurring during the Balkan War, but prefers the subcutaneous method of administration. Kocher[7] emphasizes its value in severe cases, the treatment serving to control the tonic spasms until enough antibodies have been produced to successfully combat the toxins.

Stadler[5] reported, previous to the war, two severe cases treated with magnesium sulphate, one of which terminated fatally. He collected from the literature 51 cases of various types treated by this method with a mortality of 35.5%. He contrasts these figures with those reported in large series of cases treated with serum or by other methods. The mortality of cases treated without serum was found, according to a compilation of many statistics, to be between 62% and 85%. The mortality of cases treated with serum was found to be between 39% and 64%. In cases with a long incubation period treated with magnesium sulphate the mortality was only 9%.

Eunike[9] collected 27 cases treated with intraspinal injections of magnesium sulphate, the mortality being 33%. His own mortality in eight cases was 50%, but it must be remembered that tetanus from gun-shot wounds in war has a higher mortality than under ordinary conditions.

Kümmell,[10] in a recent article, gives some interesting figures relative to the mortality from tetanus. Of 350 cases observed in hospitals near the front, 70% resulted fatally; while of those observed in base hospitals (*i. e.*, with a longer incubation period), 25% died. He recommends the magnesium sulphate treatment, but gives no statistics as to its value.

English writers give a somewhat higher mortality figure, those of Bruce[11] being 78.2% for cases near the front, and 57.7% for cases occurring in British base hospitals. In an earlier report of a smaller series of cases, Keogh[12] found a total mortality of 71.8%. Magnesium sulphate had been used only in very few of these cases, and usually by the subcutaneous method. English writers have obtained the best results with the intraspinal injections of serum.

From the reports of those who have used the intraspinal administration of magnesium sulphate, it would seem that this treatment is of great value in cases in which a fatal outcome is to be feared from spasm of the glottis or from exhaustion; and it is with the hope that this method will be more generally used in properly selected cases of the disease that these cases are reported.

I wish to express my thanks to Dr. Diriart, surgeon-in-chief of the French Red Cross Hospital, through whose courtesy I was permitted to observe the cases under his care.

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GAS GANGRENE—ITS COURSE AND TREATMENT.*

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(*From the laboratories of The Robert Walton Goelet Research Fund.*)

The research conducted in this laboratory and published recently† has led to the conception of gas gangrene that is here presented. The treatment which this conception indicates is also suggested.

The condition usually meant by the term "gaseous gangrene" may be defined as *the death of an extensive mass of muscle due to the mechanical action of gas produced from a local focus by saprophytic bacteria.* The substances from which the gas is formed are chiefly the carbohydrate-containing tissues; hence, muscle is the tissue primarily involved. The organism is, with rare exceptions, *B. aërogenes capsulatus welchii* (*B. perfringens*).

In a previous paper we have discussed the stages through which a gaseous infection may pass.[4] The first stage we have termed *dormant;* it represents the condition present in the majority of fresh wounds. We have reported finding the bacillus in 70% of all wounds examined bacteriologically at a general military hospital, and in a greater frequency in wounds examined within the first few days of injury.[3] In the first stage the bacteria are present in the remnants of dead muscle tissue. Gas may be apparent in the depths of the wound.

The second stage we have termed *the stage of gaseous distension.* This is marked by a gaseous infiltration of the healthy tissue, with retention of gas and consequent sustained pressure. A rapid increase in intramuscular pressure may quickly deprive the tissues of blood until the muscle appears as if it had been wrung dry of fluids, and the condition of gangrene supervenes.

The process may then pass into the *explosive stage* and progress rapidly, owing to the invasion of the gangrenous muscles by the bacilli. This, in turn, is accompanied or soon followed by *the stage of systemic toxæmia,* collapse, and death. In rare instances a stage of terminal bacteriæmia is reached.

From the standpoint of treatment, a study of the conditions which determine an extension of the process from Stage 1 to Stage 2 is clearly most important. It is against these conditions that treatment must be directed. After gaseous distension has occurred, the problem becomes immediately much more complicated. Many different factors suggested by others to account for the transition from the dormant stage into that of gaseous distension are insufficient to explain the sudden change:

1. It has been suggested that we are dealing with several different organisms. There appears, however, to be one distinct species—*B. aërogenes capsulatus*—which is responsible for nearly all the cases of gas gangrene.[4] It is easily identified by its morphological and cultural characteristics. Other gas-producing organisms (with the exception of *B. œdematis maligni*) have not been observed to produce extensive lesions in the muscles. *B. œdematis maligni* is not often, if ever, the cause of extensive gaseous phlegmons, although it is not rare in the wound itself. The frequent occurrence of subcutaneous œdema associated with muscle distension is probably caused by the obstruction of the deep lymphatics and veins due to the increased intramuscular pressure.

2. It has been suggested that variation in virulence explains the different forms of infection seen in the patients. All strains of *B. aërogenes capsulatus* appear to be almost equally virulent for animals, and no relationship can be established between the severity of the human infection and the strain of the organism or its virulence for animals.[3]

3. It has been suggested that invasion of the blood is responsible for the malignant type of the disease. Metastasis, however, is almost unknown, and the presence of the bacillus in the blood is very rarely to be demonstrated during life.[4]

4. It has been suggested that absorption of soluble toxic products of the bacteria breaks down the natural immunity of the patient. The exotoxin is of only slight toxicity. Systemic toxic reactions from a local limited focus are slight. Symptoms of toxæmia occur only when a very large mass of

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* Presented at a meeting of The Johns Hopkins Hospital Medical Society, February 7, 1916.

† A detailed account of some of the points discussed here is to be found in the following articles:

1. "The Use of Quinine in the Treatment of Experimental Gaseous Gangrene," Lancet, 1915, Sept. 4, p. 538.

2. "The Use of Quinine Hydrochloride Solution as a Dressing for Infected Wounds," British Medical Journal, 1915, Dec. 25, p. 923.

3. "Factors Responsible for Gaseous Gangrene," Lancet, 1916, Jan. 15, p. 123.

4. "Observations on the Pathology and Bacteriology of Gas Gangrene," Journal of Pathology and Bacteriology, 1916, XX, 384-394.

muscle tissue has been destroyed by the gas; then the putrefactive and autolytic, colliquative, necrosis induces rapid and profound toxic symptoms. The real action of the toxic principle is, we believe, that of converting healthy muscle tissue adjacent to the wound into a favorable medium for growth and gas production by the bacteria.[3]

5. It has been suggested that certain individuals fail to react to the infection, while others develop a prompt immunity. Active immunity must be established only very rarely, in any case, because the extension of the process, when it occurs, generally follows too quickly after the infection to allow time for the production of antibodies. Furthermore, as bacterial activity is limited chiefly to detached or necrotic tissues, no prompt systemic reaction is likely to result. No immune reactions could be demonstrated in the sera of animals or men who had recovered from the infection or had received prophylactic gas-bacillus vaccine. The bacillus is rarely phagocytosed in the wound. No increased resistance could be demonstrated even in animals that had recovered from a previous infection. Guinea-pigs show no variation in individual susceptibility to experimental inoculation.[4]

6. It has been frequently suggested that injury and thrombosis of important blood vessels cause the rapid invasion of the bacteria. Thrombosis of large vessels has been found in comparatively few of our cases coming to autopsy (3 out of 19), and was then probably a secondary result of the gaseous distension, and not the cause of the trouble. Ligature of the main artery to a limb probably brings about the death of the tissues through anæmia and allows of the rapid extension of the process in much the same manner as the gaseous distension.

7. It has been suggested that toxicity of the gas caused rapid necrosis of the tissues and the spread of the infection. We have shown the gas to be non-toxic for guinea-pigs.[3]

8. Frequently symbiotic relationship between the gas bacillus and certain other organisms has been credited with determining a malignant infection. There is no constant similarity between the flora of the various cases of gas gangrene.

The foregoing factors can probably be excluded as causative. Therefore, we must look to certain conditions in the wound to find the factors determining the development of a malignant condition.

In order for the infection in the dormant stage to result in gangrene in the stage of gaseous distension, two conditions seem to be necessary: first, a continuous production of gas in the wound; and, second, sustained pressure within a muscle mass following its infiltration and distension by the gas formed.

1. The continuous gas production depends on an adequate supply of dead muscle. The wound must provide this for the establishment of the saprophyte in an anaërobic medium favorable for its initial multiplication and the production of gas and toxin. Wounds made by fragments of shell and shrapnel with high velocity are especially likely to produce this condition by reason of their explosive effect on the semi-fluid muscle mass, in addition to the tearing action and the consequent separation of fragments of muscle from their blood supply. When bones are struck, the ragged splinters accomplish the result even more effectively.

The activity of the bacteria is limited almost invariably to muscle. Subcutaneous infections in animals are comparatively difficult to produce, and the invasion of the subcutaneous tissues by the bacteria is rare in man. When it occurs, it is usually in the region of the scalp or scrotum, where the skin is comparatively rich in muscle tissue. The area of subcutaneous crepitus is not, however, an indication of the extent of the infection, but is usually merely the evidence of the escape of gas from the muscles involved. It is generally after extensive damage to the deep muscle primarily invaded and after exudation into the subcutaneous tissue of the products of muscle degeneration that the bacteria are to be found growing and producing gas in this location.

2. Sustained pressure within a muscle mass depends on retention by intact muscle sheaths of the gas produced, and by the occlusion of the avenues of escape, due to the local swelling of the muscle fibers in response to the inflammatory reaction. The structure of muscle permits an easy infiltration of gas between and parallel to the fiber bundles. The same arrangement of fibers makes its escape correspondingly difficult except in a longitudinal direction, and this outlet is frequently blocked by the bulging of the fibers into the wound. This blocking of the avenues of escape for the gas is favored by various conditions. It is especially apt to occur when fracture of a long bone is present. This deprives the muscles of their splint, which would otherwise allow the longitudinal contraction of the cut fibers to tend to keep the wound open. When a fracture occurs, the contraction of the muscles closes the wound more firmly by allowing of lateral bulging. It follows, therefore, that an infected fracture is more easily drained of gas and pus when held in extension than before traction is applied.

Treatment.

If the above conclusions are correct and the transition from the first or dormant stage is dependent on the two factors—the presence of muscle débris and obstruction to the escape of the products of the bacteria growing in this débris—the treatment of such gaseous infection becomes clearly indicated. It consists in:

1. Prophylactic treatment during the dormant stage.
2. Treatment during the stage of gaseous distension.
3. Treatment of accomplished gangrene.

Prophylactic Treatment during the Dormant Stage.—This must include, first, an attempt toward the removal or destruction of the bacteria present in the wound and toward depriving them of their necessary soil, the dead muscle; second, the institution of precautionary measures against the occurrence of gaseous distension. Time is an important factor. The shorter the interval between injury and treatment, the more certain is a successful result. Thorough cleansing of the fresh wound is necessary, including the removal of all foreign bodies possible. (Under "foreign bodies" we include dirt, fragments of cloth, fragments of bone, and also any portions of muscle showing signs of necrosis.) Following the cleansing of the wound, the use of an antiseptic active against the gas bacillus is clearly indicated. For this purpose we have found a 1% solution of quinine hydrochloride to be effective clinically.[4] It

has proved experimentally, *in vitro* and in animals, to be much more active against the organism than any other solution we have tried.[1]

In connection with the antiseptic treatment, in so far as it relates to the gas bacilli, it may be mentioned that certain solutions in common use show little bactericidal power against this organism *in vitro*. Potassium permanganate and hydrogen peroxide show no activity unless used in very large amounts, and then only temporarily inhibit the growth of the cultures. It is useless to attempt to produce an aërobic condition in a piece of necrotic tissue. Carbolic acid and hypochlorite solutions stimulate the growth of the organism *in vitro*, when present in weak concentrations. Furthermore, the bacillus grows readily in a medium containing as much as 2% of carbolic acid or 50% of Dakin's solution. The use of sugar solutions for dressings should be looked upon as dangerous, as they supply one of the necessary factors, a carbohydrate, for the active production of gas by the bacilli.

Oxygen, injected subcutaneously, cannot reach the focus of infection, which is in the muscle, and it probably serves only to increase the tension of the muscles and to interfere with the circulation of the parts. Moreover, it is sure to give an erroneous idea of the extent of the gas formed by the bacteria, and so confuse the clinical picture.

The use of anti-sera and vaccines is of doubtful value, if we consider the organism as a saprophyte, which has not invaded living tissues, and the damage done to the tissues as of a mechanical nature. It is also very uncertain that the muscle-toxic, hæmolytic principle formed by the bacteria is a true soluble exotoxin for which an antitoxic serum can be produced.

The use of the cautery appears to have no logical basis, and late results of the treatment, as far as we have observed, seem merely to indicate that it furnishes foci for certain pyogenic infections of the tissue damaged by the heat.

In order to avoid the accident of gaseous distension, the following points must be considered: The wound should be kept as widely open as possible by means of a loose pack of gauze soaked in some wet dressing, preferably the quinine solution mentioned above. Any form of bandage or splint which increases pressure in the neighborhood of the wound or blocks the escape of gas, such as tight circular bandages, circular plaster casts, and so forth, must be avoided. The circular bandage bound tightly about a limb containing a fresh wound is undoubtedly frequently responsible for the development of gas gangrene. Wherever possible a gauze pad should be substituted and fixed in position with adhesive tape instead of with a circular bandage. Where fractures of the long bone are present, the limb should be put in extension as soon as possible, in order to keep the wound wide open. These points are especially important during the period of transportation of the wounded man.

Treatment during the Stage of Gaseous Distension.—Cases in this stage are frequently being subjected to a rapidly increasing intramuscular pressure. This pressure may speedily result in the production of the death of the muscle. Hence every effort should be made to recognize the first signs of distension and to relieve the pressure at the earliest possible moment. The longitudinal arrangement of the fibers composing the muscle makes it difficult to release the gaseous pressure by longitudinal incisions, and it is necessary to make a larger number of such incisions than for the release of fluid. An attempt should be made to discover the focus of necrotic tissue where the active gas production is going on, and to remove the necrotic portions. The incisions should be dressed in a manner similar to that described for the wounds during the dormant stage. Irrigation may also be practiced, if desired, with one-tenth of 1% quinine hydrochloride solution in physiological saline.[2]

The Treatment of Gangrene.—If incisions into the muscle show a pale, dry, dull pink surface, and a consistency as if wrung dry of blood and lymph, the condition of gangrene is probably accomplished. The dead muscle is then a great menace to the patient, firstly, because it will speedily become an active source of gas production by the rapid invasion of the bacilli, and secondly, because the products of autolysis of a large mass of tissue may of themselves produce a profound toxæmia. Muscle in this condition will never regain its vitality. If the patient lives, it will be found to slough out in large fragments, sometimes as an entire muscle. Hence the treatment indicated is to remove the gangrenous tissue as quickly and as thoroughly as possible. This can usually be done only by amputation, if the process is in an extremity. No attempt should be made to cover the stump with skin flaps. The transverse section of the muscle fibers allows of free drainage of gas, and, unless extensive necrosis has occurred in the muscle tissues remaining, the process is frequently checked. The presence of subcutaneous crepitus above the possible limit of amputation, or even the presence of muscle involvement above that line, does not mean that the process will continue after the operation.

Summary.—We believe that the gas bacillus can be considered in its usual form as a pure saprophyte, and that the occurrence of gas gangrene should be regarded as the result of the mechanical accident of gaseous distension. We believe that, like tetanus, it is a preventable disease. The bacillus resembles that of tetanus in its frequent occurrence in cultivated soil, its need for anaërobic conditions which determine its saprophytic nature, and its need for a local focus of necrotic tissue in order to become a danger to its host. It differs from the tetanus bacillus in that with the latter the toxin is the active factor, whereas with the gas bacillus the mechanical action of the gas is the chief thing to be considered.

As in the case of tetanus, *all fresh wounds should be considered as potentially malignant,* and all available prophylactic measures should be applied routinely. We would suggest the routine use of quinine dressings as perhaps more nearly specific than any other antiseptic. Its use is especially indicated during the first few days after injury.

Special regard should be given to any factors which may compress the limb or interfere with free drainage of gas from the wound, particularly during the dangerous period of transportation.

I take pleasure in acknowledging my indebtedness to Dr. Joseph A. Blake for his kindness in criticising this paper.

THE PROGNOSTIC VALUE OF BLOOD CULTURES IN ERYSIPELAS.

By T. P. Sprunt.

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In a series of cases of erysipelas during the past year in the City Hospital, we have been impressed with the value of routine blood cultures for the prognosis in this disease.

Five patients of the 34 showed a streptococcus bacteræmia. Of these, four died. The fifth had very few organisms in the blood, no other demonstrable complication, and recovered after a prolonged febrile course of 32 days, the longest of the series. The only other fatality occurred in a case in which a blood culture was unfortunately not made, but in which metastatic lesions suggest that a demonstrable bacteræmia existed. There was no death among the patients whose blood was sterile, though several complications were encountered, *e. g.*, suppuration, phlebitis, erysipelas migrans.

The prognosis in erysipelas is usually quite favorable. The mortality is given in most statistics as from 3 to 7 per cent in the facial type, and considerably higher in that complicating surgical conditions. Infancy, advanced age, alcoholism and complications are usually stated as indicative of a bad prognosis.

Concerning bacteræmia in erysipelas, the accepted teaching is that it is of rare occurrence.

Jochmann[1] reports only 16 instances in 463 cases, including 11 deaths and 5 recoveries. Anders[2] says: "A polymorphonuclear leucocytosis paralleling the violence of the infection occurs in this disease, but streptococci have not been found in the blood." Such statements in the most widely used reference books on Internal Medicine are so at variance with our experience in this small series that a note concerning these cases has been deemed of possible value.

In several cases we have seen patients enter the hospital with the typical history, symptoms and physical signs, with nothing to set them apart from other cases, but in which a positive blood culture has speedily given a clue to the gravity of the condition. Further, blood cultures stimulate continued and careful search throughout the subcutaneous tissues for deep-seated abscesses, which are not always easy of demonstration.

The method of making the culture was by means of the now generally familiar blood-agar mixture, the blood being obtained from an arm-vein in a sterile syringe and mixed with agar in the proportions of about one part of blood to five parts of melted agar at a temperature of 42° C. to 43° C., and poured at once into Petri dishes.

The number of colonies in each cubic centimeter of blood in the six positive cultures (five cases) was respectively 1500, 15, 4, 14, 2 and 4.

Among the 34 cases there were eight instances of suppuration, five in the subcutaneous tissues beneath the primary site of inflammation, only one of which was associated with bacteræmia. In the three with abscess formation at a distance from the erysipelatous area, bacteræmia was present in two; in the third no culture was made. Thrombosis, endocarditis, arthritis and relapse each occurred once, and bronchopneumonia twice.

The incidence of marked alcoholism in 11 cases and syphilis in 10, with the high average age of the patients, 47 years, may help to explain our rather high mortality of 14.7 per cent.

The leucocytosis was commensurate with the intensity of the infection; the average of 47 counts in non-fatal cases was 16,500, and of 11 counts in fatal cases, 26,250.

As a rule, there was a progressive rise in the leucocyte count in fatal cases and a gradual fall after the count on admission in non-fatal cases.

Abstracts of some of the more interesting cases are given below:

I. *Erysipelas (Facial); streptococcus bacteræmia; abscesses of scalp and buttock; acute aortic endocarditis; pulmonary tuberculosis.*

W. H., white, bricklayer, 57 years of age, was admitted March 28, 1916, and died April 24, 1916.

There had been no previous attack. Slight cough for several months without expectoration and occasional gastric discomfort were points of interest in the past history. He admitted the occasional use of alcohol.

The present illness began three days before admission with swelling around the left eye. By the next morning the swelling and redness had extended to the nose, and by that night had involved the right eye. The patient said he did not feel badly.

On examination, there was a typical facial erysipelas with a sharply defined border. The skin was hot, red, indurated and vesiculated over the nose, eyelids, cheeks and left ear. The fever was moderate, 102°-103° F., remittent; pulse, 100; W. B. C., 18,000.

March 30. The inflammation had extended to the right ear and to the angle of the jaw. The blood culture showed four colonies of streptococci per cubic centimeter of blood; and in the evening the patient became delirious. The Wassermann reaction was negative.

March 31. The delirium continued to such a degree that restraint was necessary to keep the patient in bed. The facial swelling had subsided and only the ears remained large and swollen. Collapse occurred during the night with recovery after strophanthin. W. B. C., 20,000.

For two days water and nourishment were administered through the stomach tube, after which the patient became sufficiently rational to make this procedure unnecessary. The lesions on the face disappeared with the exception of that in the skin over the right ear; the blood pressure rose to 120/65, and the temperature approached the normal.

April 4. The patient was quite weak and semi-delirious, and a small red area was noted on the right buttock. This enlarged, until on April 9 there were tenderness, heat and marked induration, deep seated, especially over the right gluteus maximus, and conforming somewhat in shape to that muscle. W. B. C., 25,000; the blood culture was sterile. Later the lesion over the buttock was opened and drained, as was a similar one which developed in the scalp. Pus from the former abscess showed Staphylococcus

[1] Jochmann: Mohr-Staehelin. Handbuch der inneren Medizin, 1911, Bd. 1, 726.

[2] Anders: Osler-McCrae. Modern Medicine, 1913, Vol. 1, 588.

aureus. There was a progressive downward course, high fever and death on April 24.

Autopsy 812. Anatomical diagnosis: Primary: Extensive necrosis of tissues over the sacrum; abscess of the right side of the scalp; acute vegetative endocarditis (aortic valve). Subsidiary: Proliferative tuberculosis, upper lobes; caseous bronchopneumonia, left lower.

II. *Erysipelas (Facial); streptococcus bacteræmia; cellulitis, left leg; suppuration of scalp.*

H. E., colored stevedore, aged 33 years, was admitted April 20, 1916, and died May 2, 1916.

There had been no previous attack of erysipelas. Typhoid fever, tonsillitis, venereal sore without secondary manifestations, and the occasional drinking of gin were features of the past history.

The present illness had begun five days before with malaise and pain in the back and limbs. That night the patient had a chill, and the next day the face was swollen and tender.

The lesion was typical, involving both cheeks, the nose and the lids of both eyes; vesiculation was well marked. The temperature was remittent, reaching 104° and 105° F.; pulse, 100 to 120. The mucous membrane of the nose was red and swollen; the mouth showed extensive sordes, extreme pyorrhœa and eroded teeth; W. B. C., 28,000.

April 22. The inflammation spread rapidly, involving both ears, the scalp, and practically closing the eyes. There were no signs of suppuration. The patient was delirious, talked at random, left his bed several times, and had hallucinations. A blood culture at this time was sterile.

April 24. W. B. C., 32,000; two days later, W. B. C., 30,000; the swelling of the face began to abate.

April 29. The erysipelas had almost disappeared, but there was no corresponding general improvement; a few coarse moist râles were heard at the left base.

May 1. W. B. C., 47,000. The patient was almost comatose, markedly asthenic with small, weak pulse. The blood culture showed 15 colonies of streptococci per cubic centimeter of blood. The cerebrospinal fluid was normal. A red, swollen area, discovered in the calf of the left leg was incised, and about an ounce of pus evacuated. Death occurred early next day.

Autopsy 820. Anatomical diagnosis: Primary: Erysipelas; abscesses of scalp and left leg; cloudy swelling of viscera; thrombosis in the right auricular appendage. Subsidiary: Chronic pleural adhesions; tuberculous bronchial lymphadenitis; bronchopneumonia.

III. *Erysipelas (Facial); streptococcus septicæmia; lobar pneumonia; syphilis (Wassermann); residual left hemiplegia; arteriosclerosis; hypertension.*

W. F., colored stevedore, aged 55 years, was admitted May 8, 1916, and died May 10, 1916.

There had been two previous admissions for facial erysipelas, on March 2 and on April 10, 1916, respectively. Both had been of the usual duration, with typical local signs, but with very slight general disturbance. During the second attack there was no fever and the leucocytes were 8600.

On this, the third admission, the temperature was high, 103.5° F.; the patient looked very ill; the respirations were rapid. There was a marked pyorrhœa and some redness of the pharynx. Over the lungs there was no dullness, but many fine moist râles at the right base with harsh breath sounds and prolonged expiration. B. P., 150/100; W. B. C., 26,000.

May 9. Consolidation of right middle and upper part of right lower lobes. A blood culture showed 1500 colonies of streptococci per cubic centimeter of blood. The patient died on the next afternoon. No autopsy was permitted.

IV. *Erysipelas (Leg); streptococcus bacteræmia; suppurative arthritis, right ankle; cerebrospinal syphilis.*

L. S., white, painter, aged 60, was admitted June 8, 1916, and died June 11, 1916.

He was semi-comatose and the history was not satisfactory. The temperature was 104°, the pulse 120; the respirations were of the Biot type. The face and extremities were very cyanotic; the pupils were normal in size and reaction; the general musculature was held rigidly; the neck was stiff and somewhat retracted. Numerous, short, involuntary muscular contractions occurred from time to time and any attempt at passive movements elicited protest. The right leg was deformed from an old fracture. About the right ankle, and extending upward half-way to the knee, the tissues were swollen, and the skin was hot and of a blotchy purplish red color without sharp line of demarcation. This area seemed especially tender.

On the day of admission the leucocytes were 8500, the spinal fluid showed no increase in cells, negative globulin reactions, but a positive Wassermann. The blood Wassermann was negative. Examination of the eye-grounds revealed a gray atrophy of the optic nerves. The blood culture contained 14 colonies of streptococci per cubic centimeter of blood.

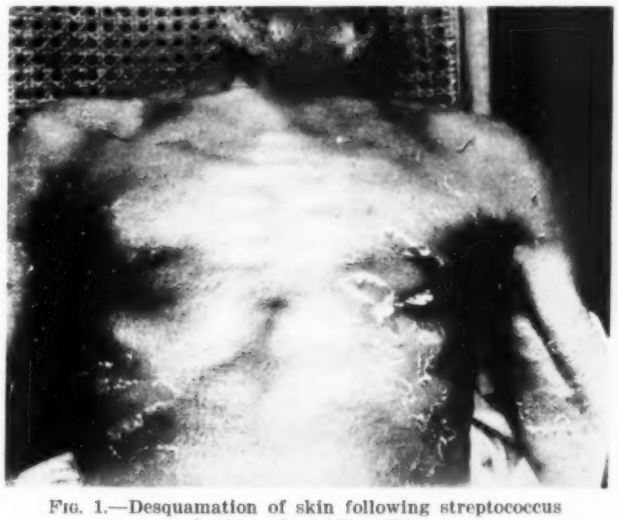

FIG. 1.—Desquamation of skin following streptococcus bacteræmia. (Case V.)

On the second day the leucocytes were 30,000. The next day suppuration was detected in the tissues about the right ankle, and two pus pockets were opened. About the same time, on the right arm at the site of a vena-puncture, and extending upward toward the axilla, a large, diffuse, soft, reddened swelling developed, and increased rapidly until death that afternoon. We considered this a metastatic infection due to extravasation of blood.

Autopsy 860. Anatomical diagnosis: Primary: Erysipelas (right leg); subcutaneous abscess extending into right ankle-joint; gangrene of skin (right arm). Subsidiary: Tuberculous bronchial lymphadenitis.

Central nervous system not examined.

V. *Erysipelas (Facial); streptococcus bacteræmia; arteriosclerosis; syphilis (Wassermann); diffuse desquamation of the skin; recovery.*

A. J., colored orderly, 50 years of age, was admitted May 14, 1916, and became afebrile June 18, 1916.

The patient was a hospital orderly, but there was no erysipelas on the ward at that time. There had been no previous attack.

The present illness began the morning of admission and was accompanied by malaise, nausea and vomiting.

He was a well-developed, muscular man, with the characteristic butterfly pattern of facial erysipelas associated with nasal obstruc-

tion and a mucopurulent discharge. There was reddening of the pharynx, diffuse pyorrhœa and a considerable degree of dental caries. Some enlargement of the epitrochlear lymph nodes was noted, and a few fine râles were heard at the right base. The pulse was regular, the vessel wall was thick and tortuous. B. P., 120/85; W. B. C., 20,000. The temperature was remittent, reaching 102° to 103° F.

May 15. A blood culture revealed two colonies of *Strept. pyogenes* per cubic centimeter of blood. By the next day the redness and induration had practically disappeared from the nose and had advanced on both cheeks with marked swelling and tenderness over both parotid regions.

May 18. W. B. C., 18,200. Wassermann positive.

May 25. The inflammation had entirely subsided, leaving only a moderate desquamation of the skin. The temperature was still elevated, reaching 103° F. on that day. The patient made no complaint except that he was being bothered too much with needles and examinations. There was no enlargement of the cervical lymph nodes, no tenderness over the sinuses, mastoids or jugular veins; the eye-grounds and ear-drums were normal; there were some irregularity of the heart and dyspnœa on the slightest exertion, but no cardiac murmurs. No lesion of the skin or subcutaneous tissue could be demonstrated anywhere. Rectal examination revealed nothing abnormal. A second blood culture showed four colonies of streptococci per cubic centimeter of blood.

During the next few days the patient ceased to protest against being kept in bed, slept or dozed lightly all the time, was easily aroused, and quite irritable, and suspicious of all who approached him. No local signs were found after careful and thorough search.

May 28. W. B. C., 22,000. The temperature gradually declined, was very little elevated on May 31, and on June 1 was normal all day, with a leucocytosis of 24,000. The next day the fever appeared again, rising to 103° F. on June 5, when the leucocytes were 15,000.

On June 15, 16 and 17 the fever was only slight, the patient's mentality became quite clear, and he began a rapid and satisfactory convalescence, of which one interesting feature was the widespread desquamation of the superficial layer of the skin in thin flakes, 1 cm. or more in diameter. This was most marked over the neck, chest, upper arms and back, and closely resembled that seen after scarlet fever (Fig. 1).

The urine showed a trace of albumin and few casts. In none of our cases was there any evidence of acute nephritis.

Summary.—In our experience, streptococcus bacteræmia in erysipelas is not an unusual occurrence. Routine blood cultures should be made in all cases of erysipelas, since the information so obtained may be of value in prognosis. Repeated cultures are indicated in severe cases.

Our experience shows further that erysipelas may be treated in a general hospital with reasonably good facilities for isolation without any great danger of ward infection.

THE HISTORY OF THE DISCOVERY OF THE SECRETORY GLANDS AND THEIR FUNCTION.[1]

By Mortimer Frank, B. S., M. D., Chicago, Ill.

The discovery of the circulation by William Harvey, in 1619, was the most important which has ever been made in medicine, and the source of most of the subsequent improvements. Supplemented with the discovery of the capillaries and that of the lymphatic system, the whole subject of anatomy and physiology was revolutionized, for now knowledge of the exchanges between the blood of the organs and tissues of the body became possible. Before Harvey's work, blood was supposed to be carried by the veins to the organs as well as from them, and the idea of the functions of the structures known as glands was based on this assumption. Hence, when the new theory came that in each organ blood flowed to it through the arteries alone, and through the organ from the arteries to the veins, and away from the organs along the veins, always in one direction, all these old views had to be changed.

Under the term "gland," the older writers included also many other organs, in fact, almost all the viscera. Of these, the three principal ones, the liver, heart and brain, were sources of blood, *spiritus vitalis* and *spiritus animalis*. The idea of "spirits" should have disappeared after the circulation of the blood was discovered, but it did not. Of the other organs, the spleen, lungs, kidneys, stomach, uterus, etc., each author placed them in this group according to his own definition of viscera which he regarded as sufficient after a logical consideration of their supposed functions. Their point of view was that of gross anatomy, and not physiology like ours. Outside this group remained the glands which were called adenai, or in Latin *glandulæ*, the salivary glands, the thyroid, the lachrymal glands, as well as the pancreas. Included in this last classification were all such round-shaped bodies which are accepted to-day as lymphatic glands.

The forefathers of modern anatomy believed the glands to be well-defined parts of the body, but without any other connection with it than that afforded by means of veins, arteries and nerves. Neither salivary glands nor pancreas were known to possess ducts, and all these varied bodies were regarded from the same point of view. Nothing was known of their function except what was given by Galen; that when they were situated at the bifurcation of vessels, which is the case with the mesenteric glands, the parotid and the thymus, then their use was to support the veins and keep them in position, or, together with fat, help to fill out spaces and give form, as, for instance, the thyroid and lachrymal glands. They could also serve for emunctory purposes whereby excretory substances could be removed from the blood or adjacent tissues.

This was the point of view before the seventeenth century, when these organs became subjected to more exact research with the discovery of the excretory ducts.

The first step was taken by Johann Georg Wirsung, a Bavarian by birth, who discovered the pancreatic duct in 1642 while working as prosector for Vesling at Padua. Wirsung's

[1] Read before a meeting of The Johns Hopkins Hospital Historical Club, April 6, 1916.

coworker, Moritz Hoffmann, claimed the discovery as his own, for in 1648 he had pointed it out in a turkey. A year after Wirsung described the duct in man he met with a tragic death by being shot as he was entering his house at night. The story states that a quarrel over the discovery of the duct was the cause of the murder, but it probably resulted from some private grudge.

In Vesling's *Syntagma Anatomicum*, it is described as an observation made by his pupil Wirsung, with reference to a canal (Fig. 1) which arises from the duodenum close to the mouth of the biliary duct and of its ramifications in the body of the pancreas. He says it is not difficult to recognize the duct, as it was often filled with a nearly colorless fluid, sharp in taste and like bile stained a silver color. He speaks of it having a valve which opens outwards and found it easy to pass a style through from the pancreas into the duodenum, but difficult to pass the style in the opposite direction. He says

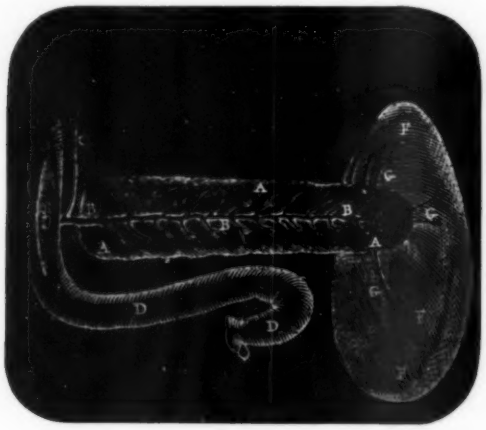

Fig. 1.

Original Figure of the Pancreatic Duct from Vesling's Syntagma.

that the duct is present in man and animals at all ages and could be neither an artery nor a vein, as it never contained blood.

The new fact so far as Wirsung was concerned remained barren, for he never followed up his discovery of the pancreatic duct by any study of the functions of the gland.

In 1654 Francis Glisson published his treatise on the liver, *Anatomia Hepatis*, and recognized its capsule which still bears his name. In that work he gave a very careful description of the anatomy of the organ, together with its form, position, weight, size, as well as its structure and function. He describes his method of tediously scraping away the parenchyma, after boiling for an hour in order to study the distribution of the vessels, as well as by maceration and by allowing the ants to eat away the soft parts (Fig. 2). It was by following the vessels uncovered in this manner from the portal fissure that he saw how the blood vessels and the branching bile duct were surrounded by a capsule of connective tissue, which we at the present day call Glisson's capsule. So far, however, as the intimate structure of the secreting substance of the liver is concerned, he must have been ignorant, as he made apparently no use of the microscope. He believed the parenchyma to be the principal part of the liver and to exercise the purpose of a filter, a fact already stated by Vesalius. All other structures are simply subservient to it. It remained for Malpighi to show that the liver was a secreting gland, and consisted of lobules or acini. He already knew the difference between conglomerate glands, *i. e.*, those with a duct as taught by Sylvius and his pupil, Steno, and conglobate or lymph glands. He thus inferred that the liver formed bile as the parotid forms saliva and is a conglomerate gland like the pancreas. Furthermore, since it is a feature of glands to possess an excretory duct, he concluded that the bile-duct is the proper excretory duct of the liver. Where Malpighi left the matter, there it remained with very little change until the past century, when chemical and physical methods were employed to solve the phenomena of living beings.

Fig. 2.

Glisson's Original Figure Showing the Hepatic Structures.

Shortly after Glisson's work there appeared in 1656, the *Adenographia* of Thomas Wharton. This publication marks an important epoch in anatomical discovery and deals not only with ductless glands, *e. g.*, the thymus, but also with his own discovery of the duct of the submaxillary gland (Fig. 3A), the duct which has since borne his name. In this treatise he describes all those organs in the body which he called glands, their nerves, blood vessels and lymphatics. The results were originally given in his anatomical lectures at the College of Physicians in 1652. In the course of his dissections he noted the similarity between the pancreas and the submaxillary gland, namely, the lobulated form, the appearance and taste of the substance. This led Wharton to believe that perhaps the submaxillary gland had an excretory duct of its own and he made his dissections on the head of an ox where the larger dimensions gave a greater chance for success. He insists that real saliva and not mucus is discharged into the mouth through this duct and attached great importance to the nerves in the formation of the saliva, the fantastic action of the *succus nervens*. He assumes that the saliva is a useful secretion in

various ways as it assists in the mastication of food, prevents a constant thirst and helps also to promote the "coctio," that is, the mixing of food in the stomach. Wharton paid scarcely any attention to the digestive uses of saliva and so failed to grasp the true significance of his important discovery. Its importance was seized upon later by Sylvius who regarded it as a type of fermentative juice and believed it to be the chief agent in bringing about the first stage of digestion.

Among all the anatomists of this century there is none more remarkable than the Dane, Niels Stensen, better known by his Latin name Steno. Born in Copenhagen in 1638, he studied medicine first in the university of his own town under the direction of Thomas Bartholin (1656), subsequently at Amsterdam under Blasius (1659), and later on under Sylvius at Leyden (1661). His studies, however, were not only medical, for he turned his versatile mind to other problems, and left an enduring mark of his genius on the science of geology as yet in its infancy.

A B

FIG. 3.

A, ORIGINAL FIGURES OF WHARTON'S DUCT OF THE SUBMAXILLARY GLAND OF A CALF.
B, STENO'S ORIGINAL FIGURE OF THE PAROTID DUCT AND LABIAL GLANDS OF A CALF.

Scarcely had Stensen, in 1661, taken his scalpel in hand when he discovered the duct of the parotid gland (Fig. 3B) which bears his name. This led to a dispute with Blasius, and Stensen went to Leyden to defend his claim to priority in a public debate with Jan Van Horne as president.

The discovery of the parotid duct was accidentally made while examining the vessels in the face of a sheep which Stensen had intended to use for dissecting the brain. A probe which was introduced into a canal that had been cut across struck with a sharp clink against the teeth and upon a closer examination it was discovered that one could go back from a natural opening on the mucous membrane of the cheek through a duct which led to the parotid gland. Sylvius found the duct in man. Later he investigated the duct of the sublingual gland, as well as those of the buccal glands, the alveolingual glands, the glands on the mucous membrane of the nose, palate and epiglottis and finally discovered the ducts of the lachrymal gland, and cleared up the problem of the secretion of tears.

Wharton had already discovered the submaxillary duct but pursued his discovery no further, while Stensen, who had learned from Sylvius the difference between the conglomerate glands, such as the pancreas and salivary glands, and the conglobate glands such as lymphatics, made use of the idea that the former were secretory glands and so must have ducts. At that time no one knew how saliva was formed and it was he who recognized that the material for the production of saliva or any other secretion is brought by the blood of the arteries to the substance of the gland. Owing to the inaccurate observations on the nature and functions of the glands, some thought that it came from the brain or the lymph and others from the papillæ of the tongue. It was Stensen who recognized the heart as muscular in its nature (1664) and a century later Haller called this work on muscle and gland, *De Musculis et Glandulis Observationum Specimen*, "a golden volume which contained the rich seed for new discoveries."

Disappointed at not receiving the appointment as professor of anatomy at Copenhagen, Stensen left for Paris and arrived there about 1664. From here he went to Italy, staying some time in Padua, and then going to Pisa in 1666. In Florence he joined the Catholic Church on the 2d of November, 1667, and ten years later he received the titular honor of Bishop of Titiopolis in Greece. The conversion of Stensen to Catholicism in no way interfered with his studies, for after his conversion he occupied the chair of anatomy in Copenhagen and wrote his epoch-making work on the geological investigations of the stratifications of rock, fossils, etc. He stayed in his native town two years and in 1674 returned to Florence to work in his new calling, theology. From this time on he devoted himself to the duties of a priest and wearing himself out in constant labor for his faith, died in 1686 at the age of 48. The fruition of this brilliant existence, compounded of so many varied and significant elements, is to be found in the results attained by Stensen in his efforts to enrich anatomical knowledge and their influence on modern investigations. Some of his observations on the nature and functions of the glands are not exempt from error, but notwithstanding this, his work rendered invaluable service to the science, and prepared the way for the farther discoveries of anatomists of his and our own times.

In 1661, the same year that Stensen discovered the duct of the parotid gland, Malpighi described the true structure of the lung. Contrary to the earlier views that the lung was a porous, spongy and frothy organ, he found that it consisted of small air vesicles which were connected with the air passages. This observation made possible a theory of respiration, but the great fact was not yet clear. It was at this time, when examining the lung of a frog, that Malpighi discovered microscopically the capillary circulation, the missing link that made Harvey's work complete. Two centuries later Marshall Hall (1831) in a paper before the Royal Society, announced his discovery of the importance of the capillaries in metabolism of the tissues.

The use of the microscope by Malpighi made his discoveries possible and they were not only numerous and important, but

ranged over both the animal and vegetable kingdoms. Engaged in studies which were in their infancy in his time, yet his investigations in anatomy and physiology extended often to minuteness of detail. A contemporary of Harvey, Borelli, Stensen, Redi, Rudbeck, and Bartholin, Malpighi was born at Crevalcore, near Bologna, in 1628, the year in which Harvey published his book on the circulation of the blood. He entered, in 1645, the University of Bologna, and took his degree in medicine and philosophy in 1653. His thesis was devoted to the works of Hippocrates, whose thoughts he endeavored to revive, but his enthusiasm was only of temporary duration for he soon became interested in the new studies of anatomy and physiology.

When only 28 years old, he became professor in his own university, but in the same year accepted a more valuable appointment at Pisa on the invitation of Ferdinand II, Grand Duke of Tuscany, who created for him a special chair of theoretical medicine. Here at Pisa he made the acquaintance of Borelli, his senior by 20 years, and the two became close friends, Malpighi absorbing the new doctrines of mathematical-physical learning and Borelli on the other hand acquiring a knowledge of anatomy. Three years were thus spent at Pisa, teaching and learning, but owing to the climate Malpighi was obliged to resign on account of his health. Going back to Bologna he took up his former duties there, though after another short interval he was invited in 1662 to occupy the chair of medicine in Messina and accepted the offer. This post again was displeasing to him and once more after four years' absence he resumed his work in his native city and remained in it until 1691. On his way home from Sicily in 1666 he made a journey to Rome where he met and made friends with Stensen. In 1691 he was summoned to Rome by Pope Innocent XII to become his physician, died there in 1694 and was buried in Bologna.

The true scientific career of Malpighi began at Pisa where he had the good fortune to become the friend and colleague of Borelli and to him he first communicated most of his researches. In 1656, he examined the liver, spleen and kidney, and came to the conclusion that all these organs were to be considered as conglomerate glands. As to his views about the liver enough has been said already.

In his tract on the spleen he cleared up many indistinct theories. He gave a careful description of its structure, of its capsule, trabeculæ and texture, and of its blood vessels. The trabeculæ he at first thought were nervous in character, but soon recognized their contractile nature, and thus showed the spleen to be not a gland either conglomerate or conglobate, but a contractile vascular organ. He ascribed to the small white lymphoid infiltrations attached to the blood vessels which he found in the spleen and which still bear his name, Malpighian corpuscles, the rôle of glands, and as he did not find any excretory duct from them, he assumed that they emptied their products directly into the blood. To this day we still speculate as to the nature of the Malpighian corpuscle of the spleen, whether it has or has not a capsule, and what is its precise function.

The great achievement of Malpighi, however, relates to his researches into the structure of the kidney. In 1662, Lorenzo Bellini, a pupil of Borelli, in a little tract, *De Structura Renum*, described the straight tubes that still bear his name, but Malpighi went far beyond this and showed that the kidney consisted of masses of Bellini's tubules arranged in the form of pyramids, since known as the pyramids of Malpighi. He showed also how in each pyramid the tubules ended in orifices at the apex. But he did more than this, he saw the convoluted tubules and pointed out in injected preparations how many of these tubules began as inflated swellings or capsules and how these capsules contained a cluster of little blood vessels and so hung on to the small arteries like apples on a tree, and now called the Malpighian tufts. He was of the opinion that these were vascular in their nature and must play an important part in the secretion of urine. He conceived that from them the urine was secreted or derived and was given over by them into the tubular structure of the pyramids, to be discharged by the ureters and so to the bladder. Here he stopped and it remained for William Bowman and Carl Ludwig to work out the rest of the anatomic and physiologic problem. In his book on the viscera, *De Viscerum Structura*, etc., he not only believed the liver, spleen and kidney to be glandular in structure, but also the cortex of the brain.

He described the lingual papillæ and regarded them as organs of taste and discovered the layer of epidermis called the rete mucosum or rete Malpighi in his honor. The point, however, which Malpighi emphasized in his investigation is not the layer which has retained his name, but the papillæ, which he is inclined to assume are in connection with and possibly constitute or contain the nerve endings, and that consequently are the real organs for the sense of feeling and as in the tongue of taste.

He saw and described the openings of the sweat glands on the ends of the fingers but whether he saw the real body of the sweat glands is not clear from his description. The labors of Malpighi above recited are those likely to be of the greatest interest at this time, but they by no means cover the ground which he traversed. His famous researches on the silkworm including its development; his great great work on embryology, *De Formatione Pulli in Ovo*, 1666, have become classic and like so many of Malpighi's other works were printed at the expense of the Royal Society.

An altogether different conception of glandular structure and physiology was advanced by Frederick Ruysch who was called to the chair of anatomy at Amsterdam while Malpighi was at Messina. A master in the technic of skillful injections, Ruysch thought that all glands are formed by the innumerable terminal branches of the blood vessels. Thus in the liver, that which was called parenchyma by Malpighi and regarded as glandular did not exist. Ruysch based his conclusions on injected specimens and believed that by scraping along the blood vessels according to the old methods the finer branches are destroyed, while on the other hand in a perfectly injected liver, one sees nothing else than the finer vascular branches. He made the blood vessels the agents instead of the aids of secretion.

Two years before the discovery by Stensen of the glands and ducts in the nasal mucous membrane, the old doctrine of catarrh from the brain was made the object of a virulent attack by Conrad Victor Schneider. He fills four thick quartos (*De Catarrhis,* 1660) with endless learning and elaboration to show that it was not the brain but the mucous membrane of the nose, which secreted the mucus discharged in disease. This highly important doctrine which seems to us now so simple and self-evident should be considered an important feature of the medical history of this period.

With the discoveries of the latter portions of the seventeenth century several familiar names are associated. Johann Conrad Peyer and Johann Conrad Brunner both born in the same year (1653) discovered the intestinal glands which bear their names.

The story of the discovery of the glands we now know by Peyer's name is interesting (Fig. 4). In 1667 he published

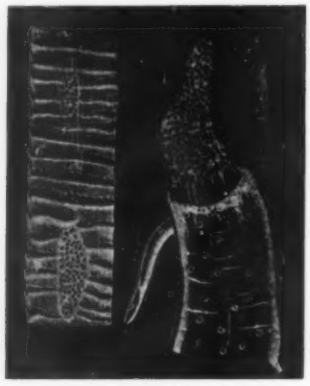

FIG. 4.

ORIGINAL FIGURE OF PEYER'S PATCHES IN THE SMALL AND LARGE INTESTINE.

his work *Exercitatio Anatomica Medica de Glandulis Intestinorum,* describing certain new glands which he says he discovered in 1673. He observed them first in the cat and stated that they are scattered over the intestine, some singly, and some in groups. He describes them as being provided each with a minute pore at its summit opening into the lumen of the intestine, from which can be pressed a little white sticky fluid. On account of the supposed duct which opened on the mucous surface, he regarded the individual small glands as secretory or conglomerate glands and not as lymphatic or conglobate. He assumes that the efficacy of the pancreatic juice becomes exhausted as the food mass descends from the duodenum, and that these glands secreted a digestive fluid which is most useful in the lower part of the small intestines. He discusses at some length in another part of the book the significance of the glands in diseases.

A few years later in 1687, Brunner described the glands in the duodenum that bear his name. In this year he became professor of medicine at Heidelberg and published his inaugural dissertation entitled, *Dissertatio Inauguralis de Glandulis Duodeni,* in which he writes about his discovery as follows: "I lowered an everted human stomach into warm water and kept it there until it commenced to shrink. Then I separated the wrinkled membrane very carefully from the layer below as far as the pylorus, and when I had gone beyond it I was fortunate to find a gland not yet discovered and in a thick mass down to the mouth of the bile duct." He speaks of these glands as yielding a juice like that of the pancreas, and called them *pancreas secundarium.* He also described the glands in different animals. In 1682 before his call to Heidelberg he published his results on the pancreas, *Experimenta Nova Circa Pancreas.* In this he made known the removal of the part of the pancreas of a dog and succeeded in keeping the animal alive for a time. According to him the digestive functions were carried on normally and the dog was about as usual and well nourished. If this be so, Brunner contends that Sylvius and de Graaf were wrong in attributing the high importance which they did to the digestive powers of the pancreatic juice. In view of the connection between extirpation of the pancreas and glycosuria in our own day, made known by von Mering and Minkowski in 1889, it is interesting to note that in one dog he observed great thirst and frequent micturition and in another a ravenous appetite. The structures responsible for the production of glycosuria in extirpation of the pancreas have been found to be a group of specialized cells, called the islands of Langerhans. Thus it would appear that the pancreas possessed an internal secretion as well as a digestive function. As to Peyer's glands, Brunner was inclined to think that they only secreted a mere mucosity and that the real digestive intestinal agent was to be found in the glands he described.

The brilliant progress of anatomy and physiology during the seventeenth century laid the foundation for a still further advance in the eighteenth century. The names of many anatomists and physiologists of these times are familiar to all of us in that the name of the discoverer still clings to the various portions of the body.

Of the microscopic anatomists of the eighteenth century, one of the most prominent was Johann Lieberkühn who studied at Jena and Leyden and later became professor in Berlin. He was a master in the injection of vessels and the first to examine injected preparations microscopically. The glands that are associated with his name he described as round white bodies in the bottom of the follicles of the mucous membrane of the small intestine. He did not find them in the follicles of the large intestine although he was acquainted with the villi and follicles of the greater gut. He was not the first to have seen these glands, and the corpuscles which he found in the bottom of the follicles were probably masses of mucus, but the possibility that he saw Paneth's granular cells in the glands, present between the epithelial cells at the bottom of the crypts cannot be excluded.

Lieberkühn's crypts were found earlier by Pio Galeotti, a physician of Bologna who saw and described them in dogs and cats. In man he observed they are somewhat obscured by the villi. He used a microscope which had a magnification of ten times for his investigations. He made his preparations by putting ink on the mucous membrane and let it soak in, then looking at the inverted intestine by transmitted light, or

made sections and examined them under the microscope. Even before Galeotti's description, Malpighi and Pechlin are said to have seen these glands.

Many other distinguished names might be mentioned in connection with the history of the discovery of the glands but the time is short, and so only a word can be said of such men as Heinrich Meibom who published a work particularly referring to the glands of the eyelids (1666); William Cowper especially memorable for the two glands which have since borne his name (1694), though really discovered by Méry in 1684; Anton Nuck whose fame is associated with Nuck's glands and who studied excellently the doctrine of the glandular system (1685); Caspar Bartholin, Jr., the eminent anatomist whose reputation has been preserved to posterity by his researches and his association especially with the glands which bear his name (1675) though they had previously been seen by Duverney in the cow, and a host of others.

With respect to the phenomena of secretion by the glands, the view of the men about 1600 corresponded to the general physico-mechanical conception of nature. Later about 1757 the doctrine of irritability was established by Haller and made to rhyme with the theories of glandular function. In this year was published the first volume of his *Elementa Physiologiæ*, and it marks the beginning of modern physiology.

During the two centuries, the seventeenth and the eighteenth, physiological inquiries, as we have seen, swayed first in one direction and then in another to explain the cause of glandular secretion. It was left, however, for the nineteenth century to throw a new light on the whole subject, and it remained for Johannes Müller one of the greatest biologists of the last or any century to work out the finer histologic anatomy of the glandular tissues. In 1830 he published his monograph, *De Glandularum Secernentium Structura Penitiori*, and upheld the view of Ernest H. Weber that the acini of the gland are the direct continuation of the ducts and showed the exact relation of the capillaries to the acini themselves. The first researches as already stated were made by Malpighi in 1665. Ruysch attributed great importance to the blood vessels of the acini, and Haller endorsed his view. Müller's monograph ranges over all the glands and deals with those both of vertebrate and invertebrate animals.

The development of the cell-theory, one of the fundamental principles of modern science, explained for all times the phenomena of glandular activity. Two names are linked together in this connection, Matth. J. Schleiden and Theodor Schwann. The former proved that plant tissues are made up and developed from groups of cells (1838), and the latter made the almost contemporaneous discovery of animal cells (1839). Thus the discoveries and rational doctrines became in the course of time the accepted conception of organic life.

Closely associated with the anatomy and physiology of the foregoing glandular system is that of the ductless glands, the thyroid and thymus in the neck, the adrenal in the abdomen, and the pituitary in the head.

The thyroid gland was almost unknown to the ancients, and so far as is known antiquity possesses but one passage which undoubtedly points to it. This occurs in a work, *De Voce*, which is attributed to Galen. In it he speaks of the glands of the larynx, "which are of a spongy nature, and the humor from them oozes out and trickles down, there being no necessity for ducts, and which have been created for the purpose of moistening and bathing all the parts of the larynx and the passages of the throat."

After Galen there is a long silence until Vesalius distinctly recognized its existence. In his *De Corporis Humani Fabrica*, 1543 (lib. vi, cap. iv) he states that "this dissection also shows two glands, one on each side of the root of the larynx, which are of large size and somewhat fungus, and nearly of the color of flesh, but rather darker and covered with many prominent vessels." Further on in the same chapter he suggests as a use for the thyroid, the moistening of the lumen of the trachea. In the second book (lib. ii, cap. xxi) he shows the thyroid in four of his illustrations of the larynx, and it appears as two round bodies, one on either side of the base. For a hundred years Vesalius' description of the organ was accepted. Up to the time that Thomas Wharton (*Adenographia*, 1656) gave it the name thyroid most writers either omitted referring to the gland, or spoke of it in the terms of the description given to it by Vesalius, "glandulas ad laryngis radicem adnatas." Wharton's was the first systematic account of the gland, and a whole chapter was devoted to it.

Giulio Casserius (*De Vocis Auditusque Organis Historia Anatomica*, 1600) accurately determined the position of the gland, and made some investigations as to the presence of an excretory duct, but concluded there was none. He regarded the thyroid as having an important part in relation to female beauty by filling out the sides of the neck.

Bartolommeo Eustachius (*Tabulæ Anatomicæ*, 1714) recognized that the two lobes are in effect one organ, and gave to the structure connecting the lateral lobes the name isthmus. Giovanni Battista Morgagni (*Adversaria Anatomica Omnia*, 1723) put an end for all time to the dispute as to the duality or singleness of the thyroid, but was of the opinion that there were minute ducts leading from the gland into the larynx. The question as to whether the thyroid possessed a duct or ducts was discussed with great animation until the beginning of the nineteenth century, when the opinion prevailed that there was no duct. With the appearance of Haller's work on physiology (1757-1766) the gross anatomy of the thyroid gland was well understood, but the case was quite otherwise in regard to the physiology of the organ. That the gland was relatively larger in women than in men was pointed out for the first time by Realdus Columbus (*Anatomica*, 1562). However, the first to definitely localize the thyroid as the anatomical seat of goiter was Fabricius ab Aquapendente (*Chirurgia*, 1619), although the Romans knew of the cervical enlargement in pregnancy (Catullus), and in endemic goiter (Juvenal), but there is no evidence to show that they associated this enlargement with the thyroid gland.

Various theories had been proposed to explain the function of the thyroid, and as a matter of fact much uncertainty still prevails at the present time. Most of the older anatomists

contented themselves with verbally repeating what others had said about its use. These for the most part regarded the thyroid as having an esthetic use in filling out the sides of the neck, or that the secretion served for the lubrication of the larynx, and so had an effect on the voice. There is probably no other gland in the body over which so many speculations have been made, and with regard to which such diverse opinions have been held, all of which were more or less fanciful.

The first to state the modern theory of the varied phenomena as applied to the glands of internal secretion was Théophile de Bordeu (1722-1776). In his *Analyse Médicinale du Sang*, published in the year of his death, he hit upon the doctrine that "not only each gland, but each organ of the body, is the workshop of specific substance or secretion which passes into the blood, and upon these secretions the physiologic integration of the body, as a whole, depends." One of the most interesting parts of Bordeu's theory is his observation of the effects of the testicular and ovarian secretions upon the organism, an important factor in the modern theory of the internal secretions, for nearly all these glands are in some way connected with the sexual characteristics of the individual.

The discovery of the glycogenic function of the liver by Claude Bernard, in 1849-57, was an achievement of no mean value. He observed that if an animal be fed on food containing neither starch nor sugar, or if it be starved, sugar is still found in the hepatic vein. The liver, therefore, besides forming bile, makes sugar, which it pours into the blood. Investigating further he washed out the blood vessels of an excised liver with water, until the washings gave no trace of sugar. On exposing the liver for a few hours to its normal temperature, and washing out its vessels again, there was an abundance of sugar. There was no denying the fact that animal cells did produce sugar. The next step was to isolate the substance from the liver, and in 1857 Bernard obtained glycogen in the pure state by his potash-alcohol process. (*Compt. rend. Soc. biol.*, 1855.) Thus he proved for all time that the liver formed an "internal secretion," which it poured into the blood, and not into a duct. It was this fact that established the theory of internal secretion as a working principle in physiology. About the same time he discovered on puncturing the floor of the fourth ventricle that he produced an artificial glycosuria (*Compt. rend. Soc. biol.*, 1849), or, as it is sometimes called, experimental diabetes (1849), which the later researches of Harvey Cushing and his associates believe to be a polyuria derived from the pituitary body.

Bernard's successor in the Collège de France, Brown-Séquard (1818-1894), by his researches on the adrenal and other glands, added much to our knowledge of this subject, and put the doctrine of internal secretion upon a firmer basis. In 1856, a year after Addison published his monograph on adrenal disease, Brown-Séquard (*Compt. rend. Acad. d. Sc.*, Paris) produced all the symptoms in different animals by the removal of the adrenal capsules. In the same year Moritz Schiff, of Frankfort-on-the-Main, found that excision of the thyroid gland in dogs was fatal, and many years later, in 1884, demonstrated that a small portion of the gland left behind, or a portion implanted in the peritoneal cavity of the animal, or by the injection of thyroid juice into a vein or under the skin or by feeding by mouth with the raw thyroid gland, prevented the fatal symptoms of tremor, spasms and convulsions in thyroidectomized animals. This led to the successful treatment of myxedema by means of thyroid extract by Murray and Howitz, in 1892. The first description of this disease in man was by Gull, in 1873; and J. L. Reverdin, of Geneva, in 1892, showed that a complete excision of the thyroid in man produced an "operative myxedema." That cretinism, myxedema and operative myxedema were one and the same thing was stated by Sir Felix Semon in 1888 (*Tr. Clin. Soc.*, Lon., 1888). Exophthalmic goiter was described by Parry in 1786-1815, and by Flajani in 1833, Graves in 1835, and Basedow in 1840, but it was not until the year 1886 that Moebius attributed the train of symptoms to an excessive outpouring of the thyroidal secretion.

In 1896 Eugen Baumann discovered iodothyrin in the body and suggested the relation of the thyroid gland to iodine metabolism, and in 1880 came the discovery by Tvar Sandström of the parathyroids (Upsala Läkaref. Förh.) which appear to have an influence upon calcium metabolism.

As has already been said, the pituitary body was regarded by Galen and the older anatomists as the source of mucous discharges of the nose, but was overthrown by Conrad Schneider in 1660. In 1778 Samuel Thomas von Soemmerring (*De Basi Encephali et Originibus Nervorum Cranio*) described the pituitary as the "hypophysis cerebri." It consists of two parts, an anterior glandular lobe (pars anterior) and a smaller posterior lobe (pars nervosa), the whole being connected with the floor of the fourth ventricle by means of an infundibulum. The anterior part secretes an eosinophile material which, according to Herring (1908), passes into the third ventricle, and thus into the cerebrospinal fluid. From the posterior part the active principles of the gland are obtained. Disease of the gland shows it to have a powerful influence on growth and metabolism. That the pituitary body is essential to the maintenance of life was proven by Nicholes Paulesco, of Bucharest, in 1908, who found that its removal was fatal to animals. He also discovered that the removal of the pars anterior was the same as the removal of the whole gland, but that excision of the pars nervosa is negative. This was corroborated by Harvey Cushing, who found, in addition, that partial removal of the anterior lobe in normal dogs produced obesity, with shrinkage of the external male genitalia. The results of experimental interference, however, are still somewhat in dispute. The same observer (1912) regards the state of acromegaly or gigantism as due to excessive activity, and that of obesity with eunuchoid changes as due to failure of pituitary secretion. Acromegalic giants have been known from remote antiquity, and John Hunter's famous chase after the body of the Irish giant O'Brien in 1783, showed that he saw the pathological importance of the specimen, which is shown in the background of Sir Joshua Reynolds' portrait of Hunter. Acromegaly was described by Saucerotte (1772), by Noel (1779), by Friedreich (1868), and others, and finally by Marie (1886), who gave the

disease its name, and in 1890 correlated it with the pituitary body.

Eustachius was the first to describe the adrenal gland, and it is placed, he says, "on the upper part of the kidney and adheres strongly to the diaphragm by a fold of peritoneum. Its substance and shape are similar to that of the kidney."

In a little monograph of 43 pages, "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules," published in 1855, Thomas Addison first recognized the characteristic symptoms now called Addison's disease, and it was this tract that induced Brown-Séquard in 1856 to reproduce the disease experimentally in animals by excising the adrenal capsules. The first investigations of the physiologic properties of adrenal extract were made by Oliver and Schaefer (1894), and by Abel of Johns Hopkins University in 1897, under the name of epinephrin. The active principle was isolated and prepared artificially by J. Takamine (1901).

The thymus was known to the Greeks, and was described by Rufus of Ephesus. As to the function of this organ, we are still very much in the dark. That it has some part in the normal growth cannot be doubted. It is large in early life and undergoes retrograde changes and becomes less and less as growth ceases. Its removal in young animals has been stated to cause retardation of growth, but Halnan and Marshall (1914) by careful experimentation on the removal of the gland in young guinea-pigs found no such effect on their growth.

The natural limits of this paper would be far exceeded by any detailed attempt to give an account of the remarkable fact that the identical effects of the ductless glands indicate that their functions are interrelated, and that they are in some peculiar way concerned in maintaining the equilibrium of the body. Nevertheless, one of the theories respecting the mechanism of this correlative status will be briefly alluded to.

Bayliss and Starling (1902) assumed that the chemical control of the body is accomplished by means of secretions, from the various organs and ductless glands serving as chemical messengers, whereby the products of a particular organ pass via the blood stream to distant parts of the body and produce a correlation upon the activities of those organs. To these chemical messengers they gave the name hormone. The only hormones of the ductless glands which have been isolated to date are adrenalin, iodothyrin and pituitrin.

When we regard the rapid and marked progress which medicine has made during the past half a century, are we not fully justified in believing that progress in the future will be even more remarkable? There remains still a wide gap in our knowledge of the human body, and as we glance at the condition of medicine in former times and reflect upon the superstition, ignorance and credulity that prevailed, we cannot help but be impressed with the vast debt we owe to our predecessors. We have learned much since their time, and are apt to make light of their labors in view of modern research, but if we could read the future we doubtless would find much to be ashamed of in our present knowledge.

DISCUSSION.

DR. HOWELL: As I listened to Dr. Frank's clear and comprehensive presentation of the development of our knowledge of the structure and functions of the glands, the thought that was uppermost in my mind was whether or not it was easier to make discoveries in the seventeenth century than it is to-day. I remember that some years ago, in a public address, a scientist asserted that in the early days of histological work it was only necessary to scratch a tissue with your thumb-nail to make a discovery. It seems as though the duct of Wharton, for example, should have been easy to find, but I suppose that it was not at that time. Will the problems that we are struggling with seem as easy to those who come after us as those of other days seem to us now? I really think that our task is more difficult. We cannot make so much use of the eye, or the eye sensitized and enlarged by the aid of the microscope. We have to depend to a larger extent upon the spiritual eye of the imagination, and that organ does not function in the same uniform and reliable fashion.

What has been the contribution of our times to this subject of the secretory organs? I suppose that the most important facts that we have added have been, in the first place, the demonstration of secretory nerve fibers to some of the glands, and in the second place, the discovery of the wonderful properties of the enzymes of the glands of external secretion and the hormones of the glands of internal secretion. But in regard to the processes controlling the formation of the secretions, I fear that we have made but little actual progress. We have attempted to apply to this problem the chemical and physical knowledge of the day, and it has not seemed to be sufficient. The processes of secretion are, in fact, processes of colloidal chemistry, and we must wait perhaps until this subject is more fully developed before we are able to penetrate further into the nature of the activities of the secreting cell.

I was much interested in Dr. Halsted's confessions in regard to the effect produced upon him by the discovery of the functions of the parathyroid gland. As I look back upon my own career as a student and worker in science and ask myself what single discovery affected me most, my impression is that I got the greatest thrill from Golgi's discovery of the wonderful structure of the nerve-cell. The news was brought to this country by Dr. Henry Donaldson, who had been working with Golgi. He had some beautiful specimens with him, but I recall that when he showed them to some of the older German histologists they were unconvinced and said you could not believe everything you saw with your eyes. To one brought up on the nerve network theory of Gerlach, those beautiful structures and the neuron conception opened up fascinating possibilities.

JOHNS HOPKINS HOSPITAL BULLETIN.

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The Mortality from Cancer Throughout the World. By Frederick L. Hoffman, LL. D., F. S. S., F. A. S. A. 1915. 8°. 826 pages. The Prudential Press, Newark, New Jersey.

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